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CHRONIC PSEUDOAPPENDICITIS DUE TO INTERCOSTAL NEURALGIA.*

By John Berton Carnett, M.D.,

PHILADELPHIA.

Appendectomy for chronic appendicitis fails to relieve the preoperative symptoms in a fairly high percentage of cases as evidenced by the follow-up reports of many capable surgeons.

Stanton[1] reported 36 per cent of failures prior to 1911 and his second series reported in 1919 gave 14 per cent of failures. Gibson,[2] in 1920, reported 555 cases of whom only 429 could be followed up, and the 429 gave 61 per cent of cures, 15 per cent of fair results and 24 per cent of failures. In a second series of 432 followed cases reported in 1924, he[3] had 283 cures, 105 satisfactory results and 41 (10 per cent) failures. Lichty,[4] an internist, in 1922, reported 40 per cent of operative failures in 400 of his patients on whom appendectomies had been performed by thirty-five surgeons. Whipple,[5] in 1923, reported over 10 per cent of failures in 509 cases.

Deaver and Ravdin,[6] in 1923, reported 500 cases but, as Bettman[7] points out, they did not confine their statistics to chronic appendicitis as this term is usually employed by other surgeons because they included 145 cases having an acute exacerbation requiring immediate operation. Many of their cases, especially the obscure ones, were studied primarily in the medical wards. Only 226 patients were heard from in the follow-up and of them 83 per cent were cured, 10 per cent were partially relieved and 7 per cent had no relief.

* Paper read before a Post Graduate Seminar of the Philadelphia County Medical Society on April 22, 1927.

Coffey,[8] in 1923, stated that 70 per cent of all cases going through his clinic who had been operated upon elsewhere for chronic appendicitis in years gone by had not been relieved by the operation.

Bettman,[7] an internist, found, in 1924, that operative failures in chronic appendicitis still averaged 30 to 40 per cent. Right iliac pain and tenderness receive most frequent mention among the unrelieved symptoms.

Stanton divided his failures (36 per cent in first series and 14 per cent in second series) into two groups. The large group was typified by the young woman who haunts the surgeon's office complaining of right inguinal pain usually associated with more or less constipation. A majority of such cases at operation present a normal appendix and an enlarged mobile cecum. In eleven years of operation, he has never cured a case of that type by appendectomy. His second group of failures were appendectomies performed in the hope of curing vague abdominal symptoms. He has found that appendectomy does not cure chronic digestive disturbances.

In Gibson's series, every patient of his 102 "unsatisfactory results" had postoperative pain in some form as the chief complaint at the follow-up examinations. Gibson advised caution in operating for chronic appendicitis on women as compared with men; on the more mature patients, particularly women; and on cases in which there is no clear and reliable history of well-defined attacks, particularly of localized pain, accompanied by nausea and vomiting. He avoids appendectomy on neurasthenics of any age or sex. As a result of following the foregoing advice, taking more careful histories, making more complete examinations and using care during operation to prevent picric acid on the skin from coming in contact with the intestines Gibson was able to reduce misresults from 23 per cent in his first series to 10 per cent in his second series. He believes there are many "liars and neurotics" among his unsatisfactory cases.

Lichty advises against making a diagnosis of chronic appendicitis unless there is a definite history of a characteristic acute attack. He finds that those patients get well if operated upon but in the absence of a previous acute attack, appendectomy begins a chain of operations to which there is no end. After operation such patients are worse than before. He has seen patients who had been operated upon fourteen times, the first operation having been done for a supposed chronic appendicitis.

In his series of 53 patients with bad symptomatic results, Whipple does not specify the nature of their postoperative complaints but lists the cases under thirteen headings according to diagnoses made in the follow-up examinations. His main groups are 21 with "neuroses of various types," 8 with visceroptosis and 6 undiagnosed. That pain was a prominent feature in his failures, however, is indicated by the only two groups in which he does not advise appendectomy: "(1) Those asthenic, ptotic individuals, belonging

to the so-called carnivorous type with long-standing history of pain and tenderness in the right lower quadrant. (2) Patients having many and exaggerated complaints, among them pain and tenderness in the right lower quadrant. These patients have neuroses of one kind or another and may either be the well-nourished or the ptotic type."

In a series of 127 patients who had not been relieved of their preoperative symptoms of chronic appendicitis by appendectomy at the hands of various surgeons from one to five years earlier, Bettman found that 55 patients (43 per cent) still had definite tenderness at McBurney's point quite as marked as ordinarily seen in unoperated patients.

After a study of their follow-up results in appendectomies for chronic appendicitis the various writers make a number of excellent observations. Lichty very properly states that the misresults are "not operative failures but diagnostic mistakes." It is not justifiable to base the decision as to whether or not the patient had chronic appendicitis upon the pathologist's study of the removed appendix. The microscopic test must be replaced by the clinical test of whether or not the symptoms for which the patient sought relief are cured by the appendectomy. If he is promptly and permanently cured or greatly relieved of his symptoms, he had appendicitis; and if he was not relieved, then his symptoms were not caused by the appendix irrespective of the extent of pathologic changes in it. In other words, the failures are cases of chronic pseudoappendicitis and not true chronic appendicitis. I have never been an advocate of the theory that gastric ulcers and biliary disease are due to appendiceal affections, hence I never adopted appendectomy as a routine part of the operative treatment of these lesions. I have occasionally removed an appendix that was easily accessible in such cases but the microscopic pathology in them did not differ from that found in symptomless appendices removed during the course of hernia operations. If toxins, originating within the abdomen, are the cause of cholecystitis and gastric ulcer it seems reasonable to believe that the primary focus is a hundred fold more likely to be a dilated boggy cecum rather than a chronic appendicitis.

Handley[12] points out that the simplest method of obtaining a microscopic birds-eye view of the appendix is to split it lengthwise, roll it up and tie a thread around it in the operating room. After fixation in the laboratory, a section across the roll enables the entire length of the appendix to be mounted on one glass slide.

A pathologist need not be unduly energetic to find some abnormality in the appendix of nearly every adult. Various surgeons have found that appendices removed coincident to other abdominal operations commonly show definite microscopic disease in 75 per cent or more. In 885 cases, in which appendectomy was performed incidental to laparotomy for some other primary cause, Lower and

Jones[13] found that in every instance the appendix gave evidence of a preceding lesion. In other words, chronic changes in the appendix are almost universal as judged by the microscope, and Bettman, therefore, suggests that if the microscope is to be the criterion as to the presence of chronic appendicitis then appendectomy should be universal. In recent years, pathologists have raised the question as to whether there is such a condition as a chronic inflammation of the appendix as the changes they find are those of a terminated past inflammation rather than a continuing present inflammation.

I believe the time is not far distant when "chronic" appendicitis will be regarded either as: (1) A nonexistent disease as claimed by many present-day pathologists, or as (2) an almost universal affection, rarely due to a preceding attack of acute appendicitis, but far more commonly due to degenerative changes which are incident to increasing age and which develop too gradually to give rise to clinical symptoms. William J. Mayo's recent editiorial on "Chronic Appendicitis"[9] refers to several of the points which have just been discussed. I have about arrived at the heretical conclusion that there is no such clinical entity as chronic appendicitis.

In the majority of the reported cases in which appendectomy failed to cure, the main symptoms before operation consisted of pain and tenderness in one form or another. Nearly all of the writers, whose names have been quoted, agree that right iliac pain and tenderness are invaluable symptoms in the diagnosis of acute appendicitis but when taken alone they are practically valueless as evidence of chronic appendicitis. For years past, surgeons have recognized the fact that appendectomy frequently fails to relieve pain and tenderness in the right lower quadrant and they have made persistent search to find some explanation for these symptoms other than the appendix. From time to time various other lesions were hailed as the probable answer to the riddle, but while floating right kidney, Jackson's membranes, Lane's kink of the terminal ileum, mobile cecum, pericecal or pericolonic adhesions, cecal stasis and dilatation, incompetent ileocecal valve, and postoperative adhesions may each cause symptoms occasionally, they, all combined, have not proved to be the common cause of right-sided chronic pain.

My first private appendectomy patient was a case of that type. A girl, aged twenty years, had had constant pain and tenderness in the right lower abdomen for two years. She was examined by various able consultants who all agreed she had chronic appendicitis. I removed her appendix through a muscle-splitting incision. She had a normal convalescence. Pain had disappeared when she left the hospital at the end of three weeks, but it recurred after another six weeks when she resumed normal activities and it persisted for the next two years. She then consulted a gynecologist who did an exploratory laparotomy and removed a grossly normal right ovary to relieve her "ovarian neuralgia," a diagnosis which

was not uncommon in those days, but has since gone into the discard. Her pain disappeared following operation, probably due to rest in bed, but recurred within two months and was still present when I next saw her two years later. I then found she had a slight lateral curvature of the spine and shortening of one leg. A $\frac{5}{8}$-inch lift was applied to one shoe following which her pain ceased and it had not recurred during the following six years.

Ever since observing her case, I have been on the alert to avoid doing needless appendectomies in cases of pseudoappendicitis. The voluminous literature on appendicitis does not give any definite method by which preoperative differentiation can be made between true and false appendicitis. The clinicians who have studied their postoperative failures are helpful in advising caution about operating on visceroptotics, neurasthenics, etc., but they do not specify a single sign or symptoms which will differentiate between true and false appendicitis in any individual case and it must be conceded that visceroptotics and neurasthenics are not immune to true appendicitis. About the only other specific advice they offer is to refrain from operating on patients who have chronic pain and tenderness in the right iliac region and who do not give a history of vomiting and nausea at some previous acute exacerbation. I have removed the appendix in certain cases of acute pseudoappendicitis in which nausea and vomiting were symptoms but in which the microscope failed to show true appendicitis, hence a history of nausea and vomiting in an earlier attack is not a differential point as between true and false chronic appendicitis. Furthermore, an undoubted earlier attack of true acute appendicitis does not exclude the likelihood of present chronic pain and tenderness being due to chronic pseudoappendicitis. Like the majority of older surgeons, I have in the past avoided operation on these cases of chronic right-sided pain and tenderness largely as the result of surgical intuition or a "hunch," but a hunch is not a very convincing argument to advance to an alert modern internist as a reason for not doing an appendectomy on his supposed chronic appendicitis patient. For years I have been endeavoring to ascertain the common cause of chronic pain and tenderness in the right lower abdomen. I believe the answer to this puzzle is to be found in the abdominal wall and not within the abdomen. None of the writers on chronic appendicitis seem to have taken into consideration the possibility, either before or after operation, that the symptoms may have been due to extraäbdominal lesions. In their various analyses, however, pain and tenderness receive frequent mention among the unrelieved symptoms.

By careful study of these cases, I have gradually replaced my former hunch with a series of tests which have proven effective in convincing medical consultants that in the majority of their suspected cases the symptoms of chronic appendicitis have been simulated by pain and tenderness situated in the anterior abdominal

wall. The customary method of palpating the abdomen only when the maximum muscular relaxation has been obtained invariably fails to disclose the parietal location of extraäbdominal tenderness. The palpating fingers have to dip more or less deeply into the abdomen before relaxed muscles offer sufficient counter resistance to demonstrate anterior parietal tenderness and because his fingers thus go deeply before any tenderness is elicited, the examiner erroneously assumes that the parietal tenderness is deep-seated and, therefore, is located inside the abdomen.

I have devised a simple bedside test to differentiate between intraäbdominal and extraäbdominal tenderness. The test for demonstrating parietal tenderness consists of palpation during a period in which the patient holds his anterior abdominal muscles as tense as possible. The tense abdominal muscles prevent the examiner's fingers from coming in contact with the underlying viscera and any tenderness that is elicited over them will be parietal in location.

The routine application of the preceding test properly carried out on all cases exhibiting abdominal tenderness demonstrates the astonishing fact that tenderness is encountered in the abdominal wall more frequently than inside the abdomen.

In examining an abdomen, I first conform to the classical advice of gaining the confidence of the patient and making gentle palpation over the relaxed muscles to discover any possible abnormality. If palpation reveals tenderness over any part of the abdomen, I never assume that it is due to an intraäbdominal lesion without reapplying pressure over the tender area while the abdominal muscles are voluntarily tensed. Tenderness which is elicited over relaxed muscles may be either parietal or intraäbdominal in origin. Tenderness present with relaxed muscles and absent with tensed muscles is due to a subparietal lesion and its cause should be sought inside of the abdomen. Tenderness which is found both when the muscles are relaxed and when they are voluntarily tensed is due to an anterior parietal lesion and its cause should be sought outside of the abdominal cavity. Parietal tenderness varies greatly in its severity in different patients and also in the same patient on different days. The tenderness is so exquisite in some patients that they clamor at the lightest touch and they are unable to wear corsets, belts or even moderately tight clothing. On the other hand, the tenderness may be so slight that it can only be elicited by very heavy pressure.

When my preliminary examination fails to reveal evidence of an intraäbdominal lesion, my further palpation becomes much more vigorous than I was in the habit of applying before becoming interested in parietal tenderness. Before stating that an abdominal wall is free from tenderness, my final examination is conducted by vigorous poking with the end of my middle finger at or near a right angle to the surface. This vigorous poking brings to light many

otherwise unsuspected cases of parietal tenderness. I have been accused of using so much roughness in my final examination that any selfrespecting normal abdomen would yield evidence of tenderness. I believe, however, that a very considerable experience with these cases justifies the amount of force I apply and I find other excellent clinicians are adopting my poking method of examining for parietal tenderness. Many patients in whom poking palpation reveals only a faint degree of tenderness at their earlier visits will present characteristic acute parietal tenderness at some visit weeks or months later.

In cases of unilateral tenderness, finger poking of corresponding areas on the two sides aids greatly in recognizing low grades of tenderness on the affected side. It is important for the patient to maintain muscular rigidity during the active stage of the finger poking. The majority of patients have a tendency to relax the abdominal muscles as soon as they experience any discomfort and the examiner must then beware that he is not misled by palpating over relaxed muscles. It is difficult to get many patients, including children and foreigners, to tense their abdominal muscles voluntarily. This can be accomplished by having the supine patient actively raise the head or better raise both heels with knees extended and keep them held above the surface on which he is lying while the palpation is being carried out. In patients with relaxed muscles, especially as found in visceroptotic multiparæ, tensing the muscles balloons out the abdominal wall. In these cases the parietal tenderness is demonstrated at a level which in relation to the normal level of the abdominal wall is considerably deeper (Fig. 1) when the muscles are relaxed, and considerably higher (Fig. 2) when they are tensed. A modification of the parietal palpation test may be employed after finding an area of tenderness over the relaxed abdominal muscles by the examiner holding his finger tips in a fixed position, perpendicular to the body surface and at the maximum depth just short of causing pain and then asking the patient to tense the abdominal muscles either by forcible contraction of the diaphragm or by elevation of both heels from the bed (Fig. 3). In this maneuver the active pressure is supplied by the contracting muscles rising against the stationary finger which serves as a point of counter pressure.

In a previous paper, I discussed "Intercostal Neuralgia as a Cause of Abdominal Pain and Tenderness"[10] and gave many details that cannot be repeated here.

Pain and tenderness of the anterior abdominal wall, especially when chronic in their duration, are most commonly due to "intercostal neuralgia" which faulty term is used, pending the invention of a better one,[1] in the sense of including all lesions of the

[1] If "parietal neuralgia" is not satisfactory (p. 587) we suggest the term "costolumbar neuralgia" as indicating the origin of the nerves involved, less misleading than "intercostal" and less offensive than "rightsiditis." [ED.]

FIG. 1.—The depth to which palpating fingers sink over relaxed muscles before parietal tenderness is elicited. Index fingertip rests on anterior superior iliac spine. Compare with Fig. 2.

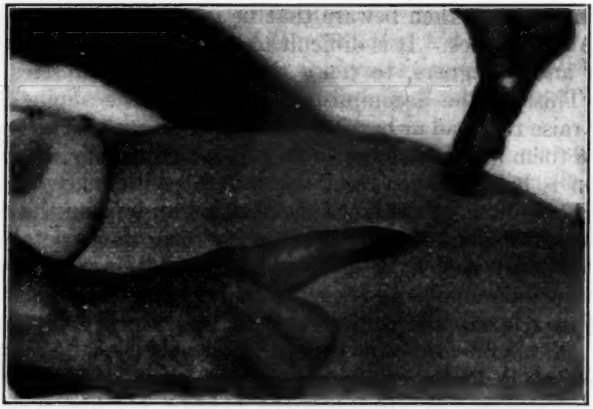

FIG. 2.—The levels at which palpating fingers demonstrate parietal tenderness over tensed muscles. Index finger rests on iliac spine. Compare with Fig. 1.

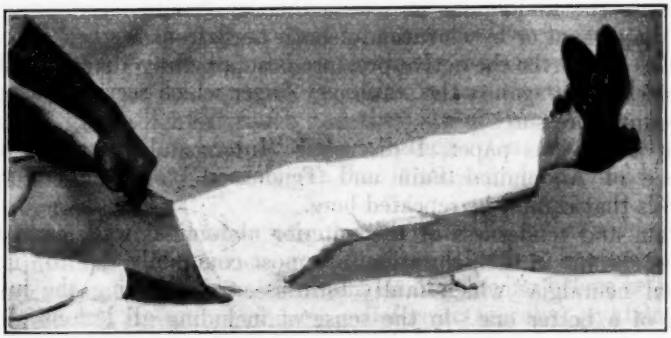

FIG. 3.—Parietal tenderness demonstrated by finger held in fixed position after indenting abdominal wall while patient tenses abdominal muscles in raising both feet from the bed.

spinal cord, meninges, vertebræ and nerves themselves which can give rise to pain and tenderness in the intercostal and first lumbar nerves. The entire nerve supply of the anterior abdominal wall comes from the lower seven intercostal and first lumbar nerves. In my previous paper, I pointed out that intercostal neuralgia is a very common affection, that it may rarely affect a single nerve, that commonly it affects several adjacent nerves on one side only (usually the right side) and that frequently all intercostals and the first lumbar nerves are involved either unilaterally or bilaterally. These and other variations presented by individual cases of intercostal neuralgia are responsible for a great diversity in the clinical pictures, some of which may closely simulate a great variety of genitourinary, pelvic and intraäbdominal lesions, including, of course, chronic appendicitis.

That the tenderness disclosed by palpation over the voluntarily tensed abdominal muscles is due to intercostal neuralgia and not to some other parietal lesion is evidenced mainly by finding tenderness: (1) By pinching abdominal skin and fat; (2) by pressure on intercostal nerve trunks; (3) by pressure over areas supplied by intercostal nerve fibers away from the abdomen.

The maximum pain and tenderness of neuralgia may be situated anywhere over the anterior parietes but it is located most frequently in the lower abdomen and, if unilateral, is usually on the right side. Parietal neuralgia is the cause of the affection which our western surgeons term "rightsiditis" and which in this paper I designate "pseudoappendicitis." In cases of neuralgia affecting mainly or only one or more or all of the tenth, eleventh and twelfth intercostal nerves and the ilioinguinal and iliohypogastric branches of the first lumbar nerve on the right side, the spontaneous pain and maximum tenderness are located in the vicinity of the appendiceal region and lead to many futile appendectomies. A fairly uniform degree of tenderness by finger-end poking both when the muscles are relaxed and when they are tense is found over an area in the right lower quadrant. This area varies in size and position and for reasons which will be discussed in a future paper does not correspond anatomically with the particular intercostal nerves involved. The tenderness usually extends more or less widely over a triangular area bounded by the midline, a transverse line from the umbilicus to the crest of the ilium, and by a third line parallel to Poupart's ligament (Fig. 4). Within the area of fairly uniform tenderness there are certain "tender points" of greater sensitiveness situated along the outer edge of the rectus muscle (Fig. 4) and which correspond to the points at which intercostal nerve branches penetrate the transversalis fascia and aponeurosis to enter the rectus muscle. In making palpation at McBurney's point the examiner is apt to encounter one of these extrasensitive "tender points," and, if not aware of its true nature, is apt to mistake it for the localized tenderness of an appendicitis. That this local tenderness is parietal

and not intraäbdominal is indicated: (1) By finding the tenderness persists when the muscles are made tense; (2) by finding similar "tender points" at higher and lower levels along the right rectus and often also along the outer edge of the left rectus muscle.

Pinching of abdominal skin and fat as a rule reveals tenderness which roughly corresponds to the outlines of the areas of spontaneous pain and of palpation tenderness.

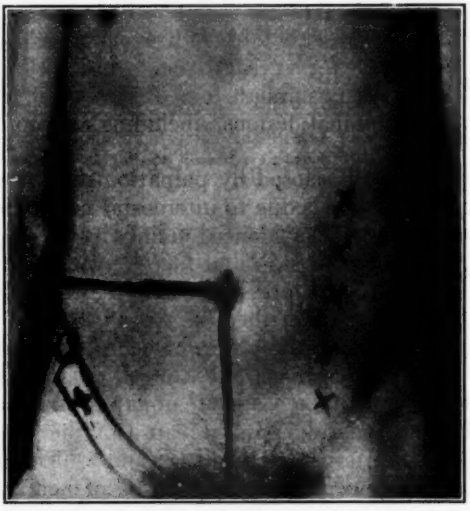

FIG. 4.—Appendix triangle. Thigh area of distribution of ilio-inguinal nerve shown by rectangle. The single cross indicates point of preference for making palpation. The row of crosses represent "tender points" along border of left rectus muscle. Anterior superior spine of ilium shown by circle.

In making the various tests to determine the degree of sensitiveness in intercostal neuralgia, it is important to contrast the sensitive area with an area of normal sensation. The examiner should exert gradually increasing pressure over the tender area by pinching or palpation up to the point where the patient manifests distress and the examiner should carefully register in his own brain the exact amount of maximum pressure he employed. He should then make a similar pinching or palpation test over a normal area, where he will find that he can apply three or four times as much pressure and cause less distress than in the first instance. The unilateral cases are the ones best suited for the novice to study these tests as he can then compare corresponding areas on opposite sides of the midline but unfortunately the majority of cases are bilateral and corresponding areas are then not available. By a study of cases of unilateral tenderness, one soon learns how to distinguish between normal sensation and bilateral tenderness very much in the same

manner as an inexperienced young practitioner soon learns from a study of unilateral rigidity to tell the difference between normal muscle tonicity and bilateral rigidity.

When the lower abdominal tenderness is bilateral, it is impossible to check the sensory findings by comparing like areas. It is then necessary to check the hypersensitive area by comparison with the upper right or left quadrant or, in the event of their being hypersensitive, with an area over the lower chest wall as it is only rarely that pinch tenderness is found in this latter area.

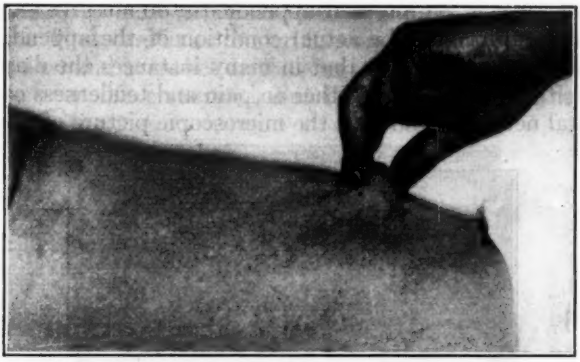

FIG. 5.—Pinch test over lower abdomen. A liberal fold of skin and fat is pinched between thumb and first two fingers.

In making the pinch test, I pick up a liberal fold of abdominal skin and fat and pinch it firmly between the balls of my thumb and first two fingers (Fig. 5), rather than attempt to pick up a tiny fold between the extreme tips of the nails of thumb and index finger as I have found several clinicians trying to do after reading the meager details of my former paper. Originally I exercised extreme care in picking up the fold not to exert a drag on the muscles nor to exert pressure against underlying muscles and peritoneum but this precaution is not necessary in the usual run of chronic cases. Because of an irreverent intern having accused me of pinching harder on one side than the other, I devised the following little test of equalized pressure for application in unilateral cases that have a flaccid belly wall. A hypersensitive area is selected about 1½ or 2 inches away from the midline. When this area and the corresponding area across the midline are grasped and squeezed between the thumb and one finger (Fig. 6) the patient complains of pain only on the affected side.

I do not test skin sensitiveness by pin prick or pin stroking, by cotton wisp or by heat and cold in my routine clinical examinations, but when they are employed they usually demonstrate hypersensitiveness over the area which is tender to pinching, although

exceptionally they reveal hyposensitiveness even when pinching is very painful.

The tender area disclosed by the pinch test is the same area which various writers describe as the area of cutaneous hyperesthesia caused by appendicitis but which I believe is caused by lower intercostal and first lumbar neuralgia and which in the vast majority of instances is present independently of appendicitis. I frequently find skin hypersensitiveness in the lower right quadrant in patients who have had the appendix removed without relief of their preoperative symptoms. The majority of the papers dealing with skin hyperesthesia as a symptom of appendicitis, do not give very extensive information as to the actual condition of the appendix found at operation and I suspect that in many instances the diagnosis of appendicitis was based altogether on pain and tenderness caused by intercostal neuralgia and that the microscopic picture of the appen-

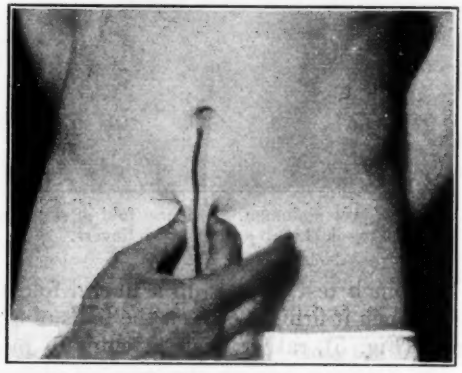

FIG. 6.—Pinch test, astride the midline.

dices did not differ from that of appendices removed coincident to other abdominal or pelvic operations. I disagree entirely with the views of Mackenzie, Head and others that skin hyperesthesia is due to a visceroparietal sensory reflex and is, therefore, indicative of underlying intraäbdominal disease. The proponents of the visceroparietal reflex confine their attention to the abdominal area of tenderness and do not seem to realize that the evidence of nerve irritability very commonly extends high up on the chest and is very often bilateral. It is impossible for me to conceive of a mild chronic appendicitis or any other visceral lesion giving rise to such a widespread "overflow" visceroparietal reflex.

Even when the hyperesthesia, as evidenced by the pinch test, is confined to the lower right quadrant it is very common to find tenderness of intercostal nerve trunks extending as high as the sixth or the fifth or even up to and including the first. The tenderness is not uniform along the nerve trunk but seems to occur in "tender

points." Palpation for nerve trunk tenderness is conducted by placing a finger tip in an intercostal space along the anterior or anterolateral wall of the chest and while making pressure upward against the lower edge of the rib the finger is carried back and forth in the interspace, as far as the slackness of the patient's skin, which adheres to the examiner's finger, will permit. Comparison is made by exerting equal or greater pressure in the corresponding interspace of the opposite side, care being taken not to be confused by bilateral nerve-trunk tenderness.

It is unusual for the patient to complain of spontaneous pain or for the skin to be hypersensitive over the rib areas. Even when the nerve trunks are quite tender, it is unusual to find any tenderness of their terminal branches on the chest wall by exerting either broad pressure over the chest with flat fingers or localized pressure by

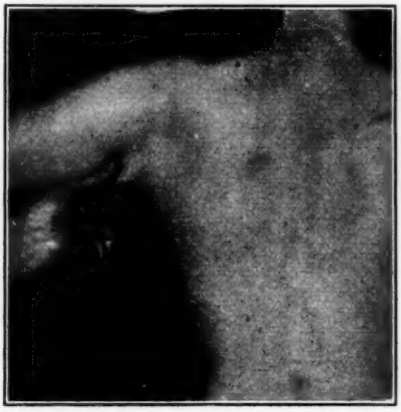

FIG. 7.—Pinch to elicit tenderness of second intercostal nerve.

sliding a finger tip firmly back and forth against the anterior surface of a rib. On the other hand, the terminal branches of the first and second intercostal nerves, which are distributed by way of the intercostohumeral nerve to the upper posterior part of the arm, are very frequently hypersensitive as demonstrated by pinching the skin, fat and muscle in the neighborhood of the posterior axillary fold (Fig. 7).

There are two other areas outside the limits of the abdomen which are very commonly found to be hypersensitive when the twelfth intercostal and first lumbar nerves are affected. Some of the terminal fibers of the ilioinguinal branch of the first lumbar nerve supply an area about 1 inch in width in the upper anterior thigh parallel to Poupart's ligament (Fig. 4). Poking pressure by a finger tip over this area will produce more discomfort than three or four times as much pressure applied over the corresponding area

on the opposite side in unilateral cases, or over a point an inch or more lower down the thigh in bilateral cases. In applying this test, I usually confine my pressure to a point just below the upper edge of Poupart's ligament and at a short distance inward from the anterior superior iliac spine (Fig. 4), so as to avoid the external cutaneous and anterior crural nerves, the femoral vessels and the hip joint.

The iliac branches of the twelfth intercostal, iliohypogastric and ilioinguinal nerves supply a V-shaped area in the buttock region (Fig. 8). All, a part, or only a point of this area may exhibit tenderness to firm poking palpation when there are neuralgic pain and tenderness in the adjacent lower abdominal quadrant. This area extends from the posterior iliac crest downward to the level of the top of the greater trochanter and lies mesial to the latter bony point. The demonstration of tenderness in this area has

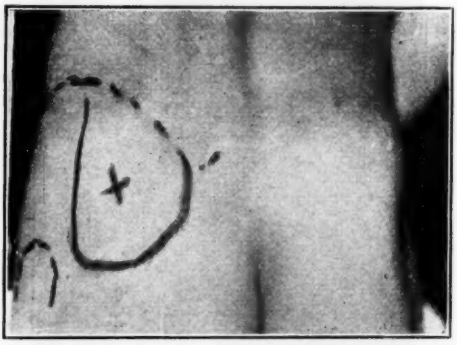

FIG. 8.—Maximum area of buttock tenderness within solid lines. Minimum area of tenderness represented by cross. Crest of ilium and great trochanter shown by dotted lines.

proven a most valuable aid in convincing consultants that tenderness at McBurney's point is parietal rather than intraäbdominal in their cases of pseudoappendicitis. The tenderness elicited in this area should be contrasted by more vigorous poking over the corresponding area on the opposite side in unilateral cases, or over an area which is almost never hypersensitive lying upward from the greater trochanter (Fig. 9).

In addition to all the preceding signs, there are often associated the symptoms and signs of a vertebral lesion which may be the underlying cause of the intercostal neuralgia.

Many cases of parietal neuralgia do not present the complete picture which I have described. Skin tenderness to the pinch test or nerve trunk tenderness, or both, may be absent even when muscular tenderness, as shown by poking palpation, is quite marked. The most constant symptom is the tenderness revealed by the poking

finger end over muscles voluntarily made rigid. In the mildest cases the only tenderness demonstrable is located in the "tender points" (Fig. 4) along the outer edge of the rectus muscle. In some of the frank cases of acute intercostal neuralgia which I have carefully observed during their period of subsidence the last sign to disappear has been tenderness limited to a single "tender point."

I want to emphasize to the novice that considerable force is necessary to demonstrate the various signs in the milder cases. The best policy for the beginner to pursue is to apply steadily increasing pressure by pinch or poke up to a point where the patient complains of distress and then test other areas by applying greater or lesser pressure.

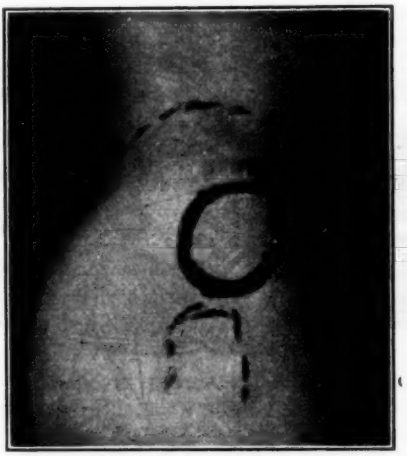

FIG. 9.—Hyperesthesia almost never found within the circle. Iliac crest and great trochanter indicated by broken lines.

The sensory nerves are distributed to three layers: (1) Skin and fat; (2) muscles; (3) preperitoneal fat or peritoneum. With relaxed muscles, the poking finger elicits the combined tenderness of all three layers. With tensed muscles, the peritoneum is protected from the poking finger and the only tenderness obtained is that present in the skin, fat and muscles. It, therefore, follows that the tenderness is usually less marked over tense muscles than over relaxed muscles.

Long-continued tenderness at McBurney's point present over relaxed muscles and absent over tensed muscles, while indicative of a lesion deeper than the anterior parietes, does not prove the presence of chronic appendicitis as in my experience this tenderness is most commonly due to a retroperitoneal lesion which, like intercostal neuralgia of the anterior parietes, is almost never considered in arriving at a diagnosis of "chronic appendicitis" by exclusion.

In a recent paper on "Chronic Strain of the Lumbar Spine and Sacroiliac Joints,"[11] to which the reader is referred for details, I described certain areas of tenderness in the posterior abdominal parietes which are commonly mistaken for the tenderness of chronic appendicitis. The chronic strains under discussion are caused by excessive lumbar lordosis and are manifested by tenderness of every part of the vertebral bodies and intervertebral disks that are accessible to palpation through the anterior abdominal wall and by a linear tenderness over the, not well-known, aspect of each sacroiliac joint located in the iliac fossa.

Very little deviation from the common method of palpating for the appendix with the balls of the fingers is required to cause the end of the middle finger to bump against the side of a tender lumbar

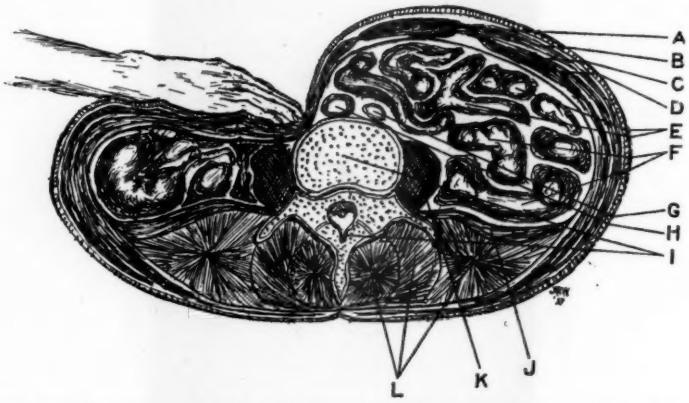

FIG. 10.—Transverse section of abdomen at fourth lumbar vertebra. The tenderness elicited by the end of finger inadvertently touching a sensitive lumbar vertebra may be mistaken for appendix tenderness.

vertebra (Fig. 10). If the examiner is not aware of what has happened with the end of his middle finger, he is almost certain to ascribe the patient's complaint of pain to tenderness beneath the balls of his fingers and hence probably due to a chronic appendicitis. The iliac fossa aspect of the right sacroiliac joint line lies directly beneath McBurney's point. In the presence of a tender right sacroiliac joint, palpation at McBurney's point is painless (unless there is the common association of anterior parietal neuralgia) until the fingers dip deeply enough to encounter the bony resistance of the joint and then the patient will evince evidence of marked distress. Fortunately this sacroiliac joint tenderness is practically always bilateral and almost invariably associated with tenderness of the lumbar vertebræ. Hence the importance of deep tenderness at McBurney's point as evidence of chronic or even subacute or acute

appendicitis is completely discounted by finding exactly the same type of tenderness in the left iliac fossa and along the lumbar spine.

Visceroptotic individuals supply the bulk of chronic pseudoappendicitis cases on whom appendectomies are performed without relief of their preoperative symptoms. Patients with visceroptosis are prone to present a variety of symptoms which simulate chronic appendicitis, but which on careful analysis can usually be classified under the three headings of: (1) Diverse digestive disturbances due to ptosis and intestinal stasis; (2) deep-seated tenderness at or near McBurney's point, due to chronic strain of the lumbar spine and sacroiliac joints; (3) intercostal neuralgia of the anterior abdominal parietes due to lumbar lordosis and possibly also to intestinal toxemia. Any one of these groups of symptoms may occur alone in any individual patient but more frequently two or all three groups are encountered at the same time.

The clinician who believes appendectomy will cure those cases of indigestion in which a definite organic lesion such as cancer, gall stones and gastric or duodenal ulcer has been eliminated and in which symptoms persist in spite of careful dietetic, medicinal and physiotherapeutic measures will find abundant opportunity to test out operative results in his visceroptotic group of patients. Moynihan expresses the dictum, that the real lesion in cases of suspected gastric ulcer is most often located in the right iliac fossa. Many clinicians continue to report excellent operative results but my own successes have been so infrequent that I never advise appendectomy as a cure for indigestion.

The clinician who believes that a constant, fixed point of deep tenderness at or near McBurney's point found week after week on palpation of the right iliac fossa, is definite proof of the presence of chronic appendicitis should make certain that exactly the same form of palpation does not reveal the same type of tenderness in the left iliac fossa before advising appendectomy. Otherwise he is likely to find that the preoperative tenderness of a strained lumbar spine or right sacroiliac joint continues indefinitely after operation.

The clinician, who believes that chronic appendicitis is the usual cause of diffuse chronic pain and tenderness in the right lower quadrant of the abdomen, should apply the tense muscle test, as well as the relaxed muscle test of palpation, in order to ascertain before operation whether the tenderness is located in or beneath the anterior abdominal parietes, or he is apt to find after operation that the chronic parietal pain and tenderness of intercostal neuralgia still persist.

With the various possible symptoms and signs suggestive of chronic appendicitis which the visceroptotic so commonly presents, she is very lucky if she passes through the hands of a snapshot diagnostician without being advised to have an appendectomy.

The symptoms and signs listed in various textbooks or systems

of surgery as being indicative of chronic appendicitis can all be found with great frequency in visceroptotics from whom the appendix has been removed.

Roentgenologic reports as to the presence of chronic appendicitis are often misleading. Various radiologists may interpret the same appendix picture by diametrically opposite opinions. The late Dr. Carman of the Mayo Clinic hit the nail on the head when he stated that since few normal appendices have been found by surgeons or pathologists the diagnosis of chronic appendicitis when based upon any form of Roentgen ray evidence is not at all hazardous. Radiologists very commonly make an erroneous diagnosis of chronic appendicitis because they find tenderness over the visualized appendix at the various sites to which it can be displaced during a fluoroscopic examination. They very commonly neglect to palpate the sites from which the appendix has been displaced or they would soon learn that the same tenderness, usually due to parietal neuralgia, persists at each site irrespective of whether the appendix is therein or elsewhere. In other words, fluoroscopic observations of tenderness moving with the appendix are absolutely valueless, unless they are coupled up with the finding that the tender areas lose their tenderness when the appendix is displaced from them. Since adopting the above suggestion, Dr. Henry K. Pancoast tells me that he very seldom finds true appendix tenderness, and regards the time-worn report of tenderness over a visible appendix unworthy of credence as an evidence of disease, except possibly in the few instances in which it is elicited in the manner mentioned above. Dr. Pancoast outlines his present views on the roentgenologic diagnosis of appendicitis as follows: "I regard the undoubted Roentgen ray evidence of an adherent appendix as the only safe sign of disease of that structure. Moreover, I do not regard the diagnosis of 'appendicitis' to be routinely within the province of the roentgenologist, whose report should deal entirely with adhesions, including, if possible, a description of the manner in which the appendix is bound and to what structures and its location. One must, be sure that the appendix is visible by films as well as fluoroscope. Its appearance may be closely simulated by partly filled ileum, sigmoid or cecum. The roentogenologist should know the extent of a previous operation, as the appendix may have been left in following rupture and localized peritonitis; and if made visible by a Roentgen ray examination, its relations would lead to a diagnosis of adhesions. The only worth-while evidence of appendiceal disease is pyloric spasm when coupled up with an adherent appendix, but even this is a suggestive rather than a positive sign."

It has been assumed and advised by many writers that a material reduction in appendectomy malresults would be obtained by abandoning the limited grid-iron incision in favor of a longer right rectus incision which would permit of more extensive exploration. In

Gibson's 102 unsatisfactory cases, there were 65 cases in which the appendix was obviously pathologic, but in 66 per cent of them he made further exploration at the time of operation and in the 37 cases in which the appendix was apparently normal, 84 per cent were subjected to further exploration at the appendectomy. Briefly, extensive exploration in 73 of the 102 patients did not avert the unsatisfactory result. It is true that an extensive incision for appendectomy may occasionally reveal an otherwise unsuspected gastric or duodenal ulcer, biliary disease, a renal or ureteral affection or pelvic disease, but Gibson's figures indicate that wide operative exploration is not a panacea for "rightsiditis." I contend that the cause for right-sided pain and tenderness should be sought by a simple bloodless exploration for signs of neuralgia in the nerves which supply the abdominal parietes, and after thus excluding pseudo-appendicitis, the gridiron incision will prove entirely adequate for the cases of true appendicitis. If the same care is exercised in applying diagnostic methods to the parietes as to the viscera, there will be no more need for making extensive incisions and explorations for chronic appendicitis than for any other visceral lesion.

Every diagnostician is familiar with many cases in which appendectomy has failed to alter the symptoms ascribed to chronic appendicitis. The big majority of the cases of that type that come under my observation show unmistakable signs of intercostal neuralgia and lengthy rectus incisions with wide intraäbdominal exploration would not have benefited their complaints.

The patients often are temporarily benefited by the rest in bed and by the psychology incident to the appendectomy, but more commonly they continue to complain of the same pain during hospital convalescence and on so informing the surgeon they receive assurances to the effect that they have confused their preoperative pains with the normal postoperative soreness of the wound and that they will be free from pain in a few days or weeks. But the original pain persists or recurs after resuming normal activities and a certain percentage of these patients are later subjected to a futile oöphorectomy, and they are lucky if they escape a third futile operation for adhesions. In my experience, intercostal neuralgia is the usual cause for multiple abdominal scars. Patients complaining of pain and tenderness atypical of intraäbdominal lesions should not be subjected to appendectomy nor, in the event of appendectomy proving futile, should they be condemned as "neurotics or liars," as many believe but only Gibson frankly so states, without their first being examined for intercostal neuralgia. The more thoroughly I study these cases the more convinced I am that they are not liars, nor fakirs, nor malingerers. While any single case may vary somewhat from the usual composite picture, or a given case may exhibit greater or lesser variations from day to day in the severity and extent of symptoms, yet all of them

react to the various tests in an entirely consistent manner. For instance, if tenderness is slight over the lower abdomen it will also be slight over the upper buttock, but if tenderness is marked over the one area it will also be marked over the second area. The most strikingly consistent feature in all these cases is the manner in which the extreme outer limits of the tender areas conform to anatomic boundaries. The malingerer has no way of knowing that the examiner expects to find tenderness away from the abdomen as in the regions of the groin, buttock and intercostal spaces and possibly also of the posterior axillary fold; nor is he aware that his tenderness, if unilateral, should not extend beyond the linea alba hence he would be exposed instantly by the tests for intercostal neuralgia. It is true that the great majority of these patients are neurotics, but that does not mean that their intercostal neuralgias are any less real affections than would be gall stones, gastric ulcer or strangulated hernia. It is interesting to note that, after becoming interested in these cases, the diagnostician lends a more attentive and credulous ear to patients complaining of unusual pain with corresponding improvement in his diagnoses along other lines.

After extensive painstaking research of patients and of appendix literature, I have been unable to find a symptom complex which warrants a preoperative diagnosis of (clinical not microscopic) chronic appendicitis and which will be relieved by appendectomy. I make the preceding statement in the face of the statistics presented in the early part of this paper. The majority of reporters of their own statistics presented them in an apologetic spirit because of their high percentages of failures, but I think they are to be congratulated for their high percentage of successes from appendectomy for so-called chronic appendicitis. I am firmly convinced: (1) that "chronic appendicitis" as ordinarily encountered under the microscope does not give clinical symptoms; (2) that the clinical symptoms that heretofore have been ascribed to "chronic appendicitis" are not caused by the appendix and are not physically cured by appendectomy. Psychic or fallacious cures are very common in my experience. I am repeatedly encountering patients who give an off-hand history of having been cured by an appendectomy for pain and tenderness of a year or longer duration. On closer questioning, they admit having right iliac "pains which are of no consequence because I know my appendix is out." When asked if the present pains are like the ones they had before appendectomy they say "No, my pains before operation were appendix pains." Then when asked how the present pains differ from the preoperative pains, they look blank at first and then finally reply. "Now that you put the question that way I cannot tell you of any difference and, as a matter of fact, I have often told some member of my family that I was glad my appendix was out because some of the recent attacks of severer pain were like the ones I had before my operation."

Figures based on such inconsistent statements can be made to prove anything. To complete the picture of inconsistency some of these patients are applying for treatment for "gas pains in the right side" and on examination all the tests I have outlined to detect pseudo-appendicitis or intercostal neuralgia prove positive.

Patients having the right-sided syndrome of chronic pain and tenderness present somewhat diversified pictures that are uniformly consistent with intercostal neuralgia but are not consistent with any other single affection.

I had hoped to include my views on acute pseudo-appendicitis within the limits of this paper but that having proven impossible they will be published in a future issue of this JOURNAL.

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FISTULA AS A COMPLICATION OF PEPTIC ULCER: WITH A SUMMARY OF THE LITERATURE AND A REPORT OF A CASE OF GASTRODUODENAL FISTULA.

BY ROBERT T. MONROE, M.D.,

BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

A FEW months ago a patient entered the medical service of this hospital who showed a very rare complication of peptic ulcer. It is the only one of its kind in approximately twenty-eight thousand medical admissions, and one of a total of 11 similar cases on record. This complication consisted of a fistulous tract between the stomach and the duodenum caused by the perforation of a chronic gastric ulcer. Thorough search of the available literature revealed many interesting cases, and, in reporting this one, it was thought that it might be of value to review in a brief way the whole subject of fistula resulting from ulcer, with as complete a bibliography as possible. Most of the articles have been carefully searched and all

fistulæ resulting from cancer, operation, wounds, or any cause except peptic ulcer have been excluded, as well as abscesses burrowing in any direction from a perforated ulcer which are sometimes termed "blind fistulæ."

By far the most common fistula due to peptic ulcer is the gastrocolic. The first case reported in the literature is probably that of Plancus in 1726, which is quoted by Morgagni in his "De causis et sedibus morborum" in 1769; Morgagni reported a similar case. According to Voorhoeve, however, the first case was reported by Haller in 1755. Abercrombie in 1828 reported a third. All were diagnosed at necropsy, but Abercrombie gave a good account of the symptoms in his patient, who lived for three months after their onset. Davies, in 1846, reported a case in which, although there was no ulcer history, symptoms of a gastrocolic fistula were present for two and a half years before death. Rokitansky reported 1 case in 1846; Willigk, 1 in 1853; Gairdner, 1 in 1855; May and Barlow, 2 in 1856; Brinton in 1857 collected 10 from the literature. In the same year Murchison collected a series of 33 instances of gastrocolic fistula, of which 10 were due to simple ulcer. Occasional cases were reported up to the end of the century, when the condition began to gain new attention and importance because of its increasing frequency. This was found to be due to the introduction of gastroenterostomy in the treatment of ulcer, with a postoperative peptic ulcer of the jejunum perforating into the colon. Czerny, in 1903, reported the first case of this kind, while von Henzel, in 1905, performed the first operation for its relief. Hilgenreiner, in 1912, collected 119 cases. In this country, Mayo and Rankin have been most influential in emphasizing the frequency of gastrocolic and gastrojejunocolic fistulæ. They found that jejunal ulcers occurred in 1 to 2 per cent of all gastroenterostomy cases at the Mayo Clinic, and that of these a little over 10 per cent formed gastrocolic fistulæ. Falta and Jonas, in 1917, described their Roentgen ray appearance. There are no adequate reviews of the subject, but those of Lion and Moreau, and Hellstrom are possibly the most complete.

A peptic ulcer may also perforate almost any other portion of the intestinal tract as well as the transverse colon. This is asserted by Welch in 1885, but no cases are given. Brinton reported a case of fistula between stomach and ileum. Hertz and Fagge, in 1914, reported the case of a woman of twenty-eight years, who, at operation, showed an old gastric ulcer which had perforated into the jejunum, and a gastrojejunal ulcer secondary to it which had perforated into the peritoneal cavity. Hickenbotham, in 1872, reported the case of a boy, aged six years, who swallowed hydrochloric acid by mistake and died of starvation two months later; necropsy showed a large ulcer at the pylorus with obstruction and perforation through the stomach into the small intestine. Gastroduodenal fistulæ are referred to below.

Fistulæ between the stomach and gall bladder, stomach and common bile duct or pancreatic duct are mentioned by Welch. Erdmann, in 1921, reported a case of duodenal ulcer perforated into a gall bladder which contained gall stones. Le Roi des Barres, in 1913, reported a case of gastric ulcer which perforated into the portal vein even after a gastroenterostomy had been performed.

Seven cases have been reported in which gastric ulcer has perforated the heart. Oser, in 1880, reported the case of a woman, aged seventy-one years, who lived three and a half days after her first hematemesis; autopsy showed an ulcer at the cardia, on the lesser curvature, with perforation through the diaphragm into the left ventricle. Brenner, in the next year, had a patient who died four days after the first hemorrhage, and an ulcer on the lesser curvature at the cardia was found, which had perforated the heart. Finny, in 1886, had a boy aged nineteen years, who had ulcer distress for four years with typical periodicity of symptoms, rheumatic pericarditis one year, symptoms of a perforated ulcer two weeks, and a copious hematemesis half an hour before death; necropsy showed the left ventricle perforated by a gastric ulcer. Chiari reported a case in 1880, and Brunniche another in 1887. Tylecote, in 1913, reported his patient, a woman aged seventy-years, who had had ulcer distress for ten months, and died suddenly in bed; necropsy showed an ulcer at the cardia near the lesser curvature, which had perforated the left ventricle. The most recent case report is that by M. Askanazy, in 1926.

Eleven other cases are recorded in which a gastric ulcer had perforated the pericardium alone. These are described by Gutmann, Graves, Mathieu, Moigard, and Pick. Pick, in 1894, collected 10 cases in which the pericardium was perforated, 4 of which had also extended through the ventricular wall (the cases above). He found perigastritis in each case, and noted that the perforation always occurred in the most anterior part of the diaphragm, on which the heart rests.

Gastropulmonary fistulæ are as rare as the gastrocardiac, 7 having been reported. Brinton, in 1857, was aware that they might occur, and there is a specimen of one in the museum of the Royal College of Surgeons of Ireland. The cases of Leyden and Juliusberge were in men, aged seventy and forty-three years respectively, and both recovered. Neusser's and Nowack's cases were in women, aged thirty-seven and nineteen years, and both died, the diagnosis being confirmed by necropsy. Robson and Moynihan in 1901 reported the case of a girl aged twenty-four years, who, after three years of indigestion and vomiting, had perforation of her gastric ulcer, and peritonitis, from which she rallied with symptoms of a subphrenic abscess in one month, and the expectoration of great quantities of pus in two months. After drainage of the abscess, the gastric fistula closed spontaneously and the patient recovered.

Friedenwald, in 1919, had a woman aged fifty-one years, who gave a typical ulcer story extending over thirty years. After one attack she had severe pain in the left upper quadrant, hiccoughs, and a cough ending in the expulsion of more than a quart of pus, and recovery in six days.

Gastrocutaneous fistulæ are more common, especially in the older literature. Several cases are noted in the Ephemerides des Curiosités de la Nature in 1754. Lieutaud reported 3 cases in 1767, and Gerard 8 in 1803. Murchison, in 1857, summarized 25 cases of gastrocutaneous fistulæ of which 12 were due to ulcer. Brinton stated that there were 20 known cases in which perforation resulted in a chronic local abscess with final perforation of the abdominal wall. More recently Kronheimer reported 1 case in 1899, Althorp 1 in 1901, and Forgue, Chauvin, and Vinon 1 in 1919.

Ten cases of gastroduodenal fistula are reported in the literature. Cruveilhier reported a case of an hour-glass stomach, with a gastric ulcer which had perforated into an "extra stomach," which in turn opened into the duodenum. Rokitansky explained the formation of the fistula in his case by assuming that a duodenal ulcer and a gastric ulcer came together over the underlying pancreas and were eventually joined. Murchison found 3 more cases reported by Barlow, Barclay, and Dittrich. Houel reported 3 cases. Thierfelder reported a case of his own and referred to others in the literature. Welch wrote in 1885, "By extension of the ulcerative process abnormal communication is established between the left and right half of the stomach, or between the stomach and duodenum. In either case, the right half of the stomach is often converted into a large, blind diverticulum, the digested food passing through the abnormal opening. Gastroduodenal fistulæ are more frequent with the third than with the first part of the duodenum." The case of Casellas (1926) is the only one that I have found since that time. He examined roentgenographically a patient who gave no ulcer history, other than some gastric distress, and found a large niche on the lesser curvature of the stomach, which connected with the duodenum.

The following case is reported as one more instance of gastroduodenal fistula.

Case Report. C. P., M 28709, a housewife, aged fifty-two years, entered the Peter Bent Brigham Hospital October 11, 1926, complaining of stomach trouble. Her first admission was June 6, 1919, with the same complaint. Her family history was negative. She had had "anemia" at the age of sixteen years. She had one miscarriage, but no other pregnancy in a married life of twenty-seven years; the menopause occurred at forty-five years. Her past history is otherwise irrelevant.

In 1919, she stated that her stomach trouble had begun an indefinite number of years ago with attacks of upper abdominal pain, associated with nausea, vomiting and jaundice. In the intervals she was distressed by indigestion, belching, and sour eructations. These symptoms led her to

FIG. 1.—C. P., No. 11716: Showing the hour-glass appearance of the stomach and the gastrojejunostomy. The gastroduodenal fistula is well shown.

be operated upon in a hospital in a near-by city in June, 1917. The gall bladder with stones was removed, according to the hospital records. The surgeon found "a mass on the posterior wall of the stomach, the size of an adult's fist, involving the pancreas. Glands in the lesser omentum. Diagnosis was inoperable carcinoma of the stomach." She left the hospital in good condition, but soon began to have attacks of dull epigastric pain and aching in the left upper quadrant. These would last a few days, with frequent remissions of several weeks' duration. They increased in severity until she was unable to eat more than a moderate amount of food without regurgitation. She also noticed a tender lump in the epigastrium which always disappeared after vomiting. The pain was not related to meals but frequently awakened her in the early morning. It was relieved by food and soda, but best by vomiting. "Food feels as if it got as far as the stomach but could go no farther." She once noticed in the vomitus food she had eaten three days before. Three weeks before admission she passed a tarry stool.

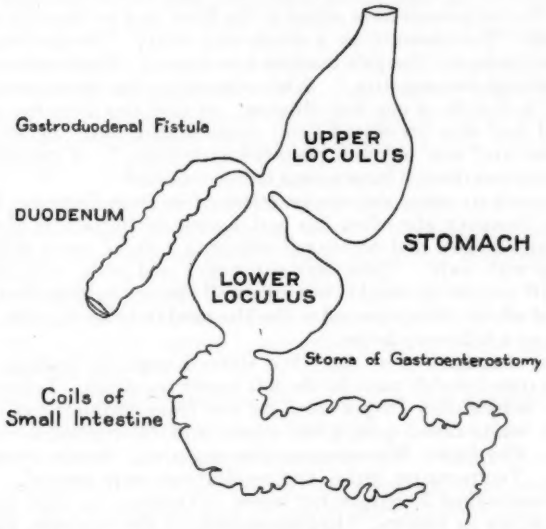

FIG. 2.—Sketched from the accompanying radiogram, showing the chief landmarks in outline.

Physical examination showed a well-developed and fairly well-nourished woman. The teeth were in fair condition. The lungs were clear, the heart negative, blood pressure 140, systolic; 80 diastolic. There was a distinct elevation of the left half of the epigastrium, over which were seen rather active peristaltic waves; no definite mass was palpated. Laboratory findings included hemoglobin, 81 per cent; red blood cells, 4,700,000; white blood cells, 5600; smear and differential normal; urine negative. The blood Wassermann test was negative. Stools gave a benzidine reaction for occult blood (single plus). Gastric analysis showed 34 free HCl and 62 total acid in the fasting contents, with nothing abnormal in the microscopic examination. Three specimens withdrawn at forty-minute intervals after a test meal showed free HCl valves respectively of 10, 15, and 23. The temperature was normal save for an occasional rise as high as 100. Pulse and respirations were normal.

Roentgen ray examination showed the stomach high, fixed, atonic. An incisura on the greater curvature extended nearly to the lesser curvature, where there was also a projection. Near this, barium was seen to pass apparently into the small intestine. Peristalsis was sluggish and reversed. The stomach was thus divided into two pouches, the upper one partially overhanging the lower. Practically the entire six-hour meal was still in the stomach, and at the twenty-four-hour observation the stomach still contained the major portion of the barium given the previous day. Sphincter duodenum, and antrum were not seen. The remainder of the intestinal tract was negative.

A diagnosis of chronic gastric ulcer was made. At operation the surgeon noted extensive adhesions to the transverse colon and omentum. "The pyloric antrum was drawn up and to the left, to the under surface of the left lobe of the liver, to which the whole lesser curvature of the stomach was very strongly adherent. A large area beginning at the lesser curvature and fading away in all directions was very markedly indurated. The whole lesion constituted a mass which might very well be mistaken for malignant disease. No metastases were noted in the liver, and no discrete carcinomatous glands. The stomach as a whole was small. The pylorus appeared normal and patent. The gall bladder was normal. Exploration of the rest of the abdomen was negative." While separating the lesser curvature from the liver "a bubble of gas was obtained, so that the ulcer has completely perforated and was prevented from extravasating only by its adhesions to the liver and also to more posterior structures." A posterior gastroenterostomy was done, a large stoma being obtained.

For the next six years she was practically free from distress. During the past year, however, she often has had a sense of fullness in the stomach, with gas and nausea and occasional vomiting. Relief came with belching, sometimes with soda. There was never any real pain. She thought she had lost 10 pounds in weight, but was well enough to participate actively in all social affairs. She returned to the Hospital October 11, 1926, for study, in answer to a follow-up letter.

Physical examination at this time showed negative findings as before, save for a questionable mass in the left upper quadrant. Laboratory findings were hemoglobin 78 per cent by the Dare method; red blood cells, 4,520,000; white blood cells, 6200; smear and differential, normal; urine, negative. The blood Wassermann was negative. Stools were benzidine negative. Temperature, pulse, and respirations were normal.

A gastrointestinal Roentgen ray series on October 11, 1926 was reported by Dr. Sosman as follows: "Reëxamination of the stomach showed it to be small, high, and hypertonic, with a definite hour-glass appearance. On the lesser curvature side, in the neck of the hour glass, there is a small projection, and the barium apparently empties from this into a loop of the intestine, which is probably duodenum. There is, in addition, an opening from the bottom of the lower pouch into the jejunum, through which most of the barium empties rapidly and well. There was no six-hour residue. The duodenal cap could not be identified. Motility was normal. The cecum and appendix showed nothing unusual. Impression: Gastric ulcer; hour-glass stomach; gastroduodenostomy (probably spontaneous); gastrojejunostomy."

Seven hours after a "motor meal" was given, 64 cc. of clear, reddish-yellow fluid without food residue were withdrawn from the stomach; it showed on testing a benzidine reaction ++++; free acid 0; total acid 10. It was considered that the tube might not have reached the lower pouch of the stomach, and that the anacidity was due to the fluid not being obtained from the acid-bearing portion. Under the fluoroscope, the small tube was again passed and its position in the upper pouch was noted. It could not be passed beyond the hour-glass constriction, and the aspirated

fluid again showed no free HCl. The patient was then given several yards of silk thread to swallow. The next day the small tube without the metal olive tip was successfully passed over this as a guide into the lower pouch, and its position was checked by fluoroscopy. The aspirated fluid showed only a trace of free Cl.

The patient improved considerably upon rest in bed, small meals and small doses of alkali. In view of her good condition and prolonged history, cancer was thought improbable. A surgical consultant saw no indication for operation. She was discharged with advice to take five small meals a day, and alkali occasionally for distress. A month later her husband wrote that she was symptom-free and gaining in weight.

Comment. There are several features of this case which are worthy of comment. Her first operation was done because of symptoms pointing to disease of the gall bladder. No ulcer symptoms were elicited. Yet a gastric ulcer was present which had caused so much inflammatory reaction that a diagnosis of inoperable carcinoma of the stomach seemed definite. The same appearance was present at the second operation two years later, when the mass was more closely examined and its true nature discovered. It is also remarkable that before the second operation she had no severe attacks of pain—chiefly, difficulty in handling ordinary amounts of food—yet exploration showed that the ulcer had perforated through the stomach wall. Again, over a seven-year period free from unusual pain, the ulcer had perforated the duodenum, this, moreover, in spite of a gastroenterostomy done for its relief. She is not a phlegmatic person whom one would call insensitive to stimuli, but a highly strung, nervous type, actively engaged in church and dramatic work.

The hour-glass appearance of the stomach was present in 1919 as seen by Roentgen ray examination and at operation. But the scar tissue causing this contraction must have been considerably less than in 1926, for no special contraindication was seen against placing the gastroenterostomy opening in the lower pouch of the stomach. Her symptoms at present seem due to the difficulty encountered in the passage of food through the stomach. Food passes through the gastroduodenal fistula easily, but slowly past the indurated area. The stoma formed in 1919 functions well. The only operative measure suggested now is an attempt to make a new gastroenterostomy, using the upper pouch of the stomach. The surgeons were reluctant to attempt this because of the obvious difficulties of the situation. Her symptoms seem to arise wholly from mechanical diminution of the capacity of her stomach and she is relieved on meals which are small enough to handle.

The finding of a normal gall bladder at the second operation, when this organ was reported as removed at the first, is unexplained. The achlorhydria may be the result of a chronic gastritis, or may suggest that carcinoma is developing. Her appearance is strongly against the latter.

Summary. Fistulous communication between the stomach and other internal organs or the body surface resulting from chronic peptic ulcer is one of the rare complications of that disease. It is sufficiently common, however, to warrant more attention than it has received. Surgeons recently have stressed the increase in gastrocolic fistulæ since the introduction of gastroenterostomy as a treatment of peptic ulcer. A survey of the literature shows the relative incidence of fistulæ in other regions.

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CANCER OF THE ESOPHAGUS.*

By Julius Friedenwald, M.D., Waitman F. Zinn, M.D.,

and

Maurice Feldman, M.D.,

BALTIMORE.

(From the Gastro-enterological Clinic of the Department of Medicine, University of Maryland, Baltimore.)

Carcinoma of the esophagus is not an uncommon affection occurring, however, less frequently than cancer of the stomach.

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Gauthier[1] observed it 18 times in 300 cancers; Lebert[2] in 13 instances in 471 cancers; Zenker and Ziemssen[3] noted it 19 times in 507 autopsies. Mathieu and Dobrovici,[4] observed 58 cases of cancer of the esophagus and of the cardia to 123 of the stomach, a proportion of 1 case of cancer of the esophagus to 2 of the stomach. Lamy[5] gives the following findings in 410 cases:

TABLE I.

	Cases.
Carcinoma of the esophagus	104
Carcinoma of the cardia	30
Carcinoma of the stomach	232
Carcinoma of the intestines	21
Carcinoma of the rectum	23
Total	410

According to Gutman and Held[6] of all cancers, 5 to 7 per cent are noted in the esophagus, although Portis[7] even considers this percentage too low and places it at 20.

Turner[8] observed 140 cases of his own occurring between 1913 and 1919, and Vinson,[9] 154 from 1919 to 1921 at the Mayo Clinic.

Our study of cancer of the esophagus is based upon a series of 128 cases occurring in our clinic. In a group of 600 cases of carcinoma of the gastrointestinal tract the following frequency was noted.

TABLE II.

	Cases.
Carcinoma of the esophagus	128
Carcinoma of the stomach	408
Carcinoma of the intestine	12
Carcinoma of the rectum	52
Total	600

Age. The disease is usually observed between the fortieth and sixtieth years, although it has been noted in young individuals; 1 at the age of fourteen years by Guisez;[10] at nineteen years by Jackson;[11] at twenty-two years by Tilley;[12] at twenty-three years by Stewart;[13] at thirty-one years by von Hacker[14] and ourselves; at thirty-four years by Kraus[15] and by Vinson.[9]

In Turner's[8] series the youngest observed were in 2 females aged twenty-eight years. The following, taken from Turner, presents the average age incidence of this disease in the two sexes. Number of cases, 42; males, 30; average age incidence, 55; female, 12; average age incidence, 48. According to Kraus 35 per cent of the cases occur between the fiftieth and sixtieth years. In our series of 128 cases the ages ranged from thirty-one years to seventy-six

years. The following table presents our 128 cases arranged according to age:

TABLE III.

Years.	Number.
30 to 40	2
40 to 50	19
50 to 60	61
60 to 70	39
70 to 80	7
	128

Sex. The disease is far more frequent among males. Lamy[5] observed 20 females in 134 cases (a ratio of 1 female to 6 males). In Jackson's[11] series the proportion of males to females is almost 9 to 1. According to Turner,[8] cancer of the upper third of the esophagus is noted more frequently in females and in the lower third in males. Of 42 of his cases, 30 occurred in males and 12 in females. In the 154 cases of Vinson,[9] 127 were in males and 27 in females; a proportion of 5 to 1; of 772 cases collected by Kraus,[15] 584 occurred in males and 188 in females. In 125 autopsy reports of this disease studied by Blauwkuip,[16] 112 occurred in males, and of Buchbinder's,[17] 145 cases only 10 were females.

In our 128 cases there were 106 males and 32 females, a proportion of 5 to 1. The following table presents our cases arranged according to age and sex:

TABLE IV.

Years.	Male.	Female.
30 to 40	1	1
40 to 50	15	4
50 to 60	49	12
60 to 70	36	3
70 to 80	5	2
	106	22

Location of the Growth. Malignant disease of the esophagus is more apt to affect those sites which present a physiologic narrowing of the lumen, possibly due to the greater irritation produced by the passage of food at those areas, that is, the entrance to the esophagus, and the aortic, bronchial and diaphragmatic constrictions. In a postmortem examination of 31 specimens of cancer of the esophagus. Turner[8] notes the following observations. In 5 specimens the tumor involved the pars laryngea pharyngis; in 5 the extreme upper end of the esophagus extending downward; in 3 it was situated in the cervical esophagus. In 18 specimens of intrathoracic tumor 4 were situated at the level of the aortic constriction, 10 at and immediately below the level of the bifurcation of the trachea and 4 at the diaphragmatic area and extreme lower end of the esophagus. In 140 of Turner's cases 98 involved the pars laryngea pharyngis with or without involvement of the esophagus; 19 the cervical esophagus;

9 the level of the tracheal bifurcation; 14 the lower end of the esophagus.

Von Hacker[14] notes that in 131 cases of cancer of the esophagus 13 occurred in the cervical area, 53 at the tracheal bifurcation, 36 at the hiatus and 29 at the cardia. According to Kraus,[15] of 857 cases of esophageal cancers collected, 158 occurred in the upper third, 302 in the middle and 397 in the lower third. Of Blauwkuip's[16] 123 cases observed at autopsy the upper third of the esophagus was involved in 28, the middle third in 51, and the lower end in 44. According to Starlinger,[18] of 132 cases 29.5 per cent occurred in the upper third, 45.4 in the middle and 25.1 in the lower third.

Vinson[9] has confirmed Turner's findings, that is, that the location of the lesion varies as to sex. According to his observations, 16 of the 27 females had their lesion at the upper third, while in 64 of the 127 males it was situated low in the esophagus. In our series of 128 cases the location of the growth was determined in 115 instances; of these 5 were observed in the upper third of the esophagus, 39 in the middle third and 71 in the lower third.

Pathology. The squamous-celled epithelioma and adenocarcinoma are the most common varieties of growths of the esophagus, representing over 90 per cent of the tumors of this region. Occasionally sarcomata of various types and other forms of growths are encountered. Carcinoma of the esophagus is usually primary, though occasionally secondary involvement from extension of the disease from the cardia, the pharynx or the thyroid has been observed. When the involvement occurs as an extension from the cardia the growth is of the adenocarcinomatous type.

Ordinarily but one tumor exists, though the presence of a second growth some distance from the first has been noted. The involvement is at first superficial, and confined to the mucous membrane, embracing but a small area, but as the growth becomes more extensive it encircles the tube and may spread in the direction of its long axis. The area becomes ulcerated and with the extension of the tumor a large part of the esophagus may become involved. Thus, according to Buchbinder,[17] from an autopsy study of 51 cases of carcinoma of the esophagus, one-third of the esophagus was involved by the growth. In the very late stages, when the esophagus is finally surrounded, encroachment upon the lumen occurs and symptoms of obstruction are produced. Slight dilatation and frequently hypertrophy of the esophagus take place above the obstructed area, the enlargement being the more extensive the lower the situation of the stenosis.

The tumor invades the muscular coat of the esophagus and connective tissue coat and other organs in its immediate vicinity. Not uncommonly adhesions take place between the esophagus and other organs. The cervical glands frequently become infiltrated and at times an involvement of the left supraclavicular lymphatic

glands is observed as an early manifestation of this disease. Of 117 cases reported by Turner[8] enlarged glands were noted in 46 instances; in addition, involvement of the surrounding cellular tissue and lymphatic glands take place and at times involvement of the recurrent laryngeal nerve of the sheaths of the large vessels and even the vessel walls. Mediastinal involvement is not infrequent. The wall of the trachea or larynx may be attacked and perforation take place into the trachea. Secondary involvement of the thyroid is a complication occasionally noted as well as metastases into the lungs, pleura and spine.

Due to ulceration, perforation may occur into the left bronchus, less frequently into the right, into the lungs or aorta. According to Zenker and von Ziemssen,[3] of 120 cases of perforation of the esophagus, 26 occurred into the right and left bronchus, 21 into the trachea and 23 into the lungs. Occasionally perforation takes place into the pericardium. Ulceration may also lead to hemorrhage by causing erosions of bloodvessels, which may be the immediate cause of death.

Symptomatology. Janeway[8] has especially called attention to the early symptomatology of cancer of the esophagus. The premonitory signs are extremely vague and uncertain. The patient frequently complains only of unusual sensations in swallowing and of a lump rising into the throat, even though the actual act of deglutition may as yet not be interfered with. In addition, there may be present a slight discomfort in the back or beneath the xyphoid cartilage, shoulders or abdomen; cough, hiccup and increased mucous secretion in the throat. Many of these symptoms are usually considered as purely nervous in character, and but slight importance is often attached to them, until the more serious manifestations of the disease appear. A prominent and early sign of the disease is dysphagia which, at first, is usually intermittent, disappearing often for a considerable length of time before becoming permanent, at first being only occasioned by spasm. Associated with the spasm even in the early stages of this disease, due to ulceration, regurgitation of small amounts of blood may now and then be observed, and occult blood may be noted in the stools. Dysphagia is rarely absent, though the growth may even assume on the other hand considerable proportions without the occurrence of this symptom. Following the dysphagia, pain soon manifests itself, which is usually noted at the seat of the obstruction; though it may be referred to other parts of the esophagus, chest, or even to the back, and may occur at times without dysphagia. Dysphagia was present in 112 of our 128 cases (87 per cent), while pain occurred in 96 cases (75 per cent) and simple discomfort only in 8 cases (6 per cent). Cough and hoarseness are often prominent signs. Cough which usually appears late, may come on early and reveal

itself before other signs are manifested. The following case is of interest in this connection:

G. C., male, aged sixty-two years, first consulted us for indigestion and a loss of 30 pounds in weight. He had enjoyed good health until three months ago when a cough began to manifest itself, soon followed by hoarseness which he attributed to a cold. Gradually indigestion appeared in the form of pressure and fullness in the epigastrium, nausea and loss of appetite. Neither dysphagia nor pain were noted. On physical examination, no lesions were detected either in the lungs or heart. A fluoroscopic examination of the

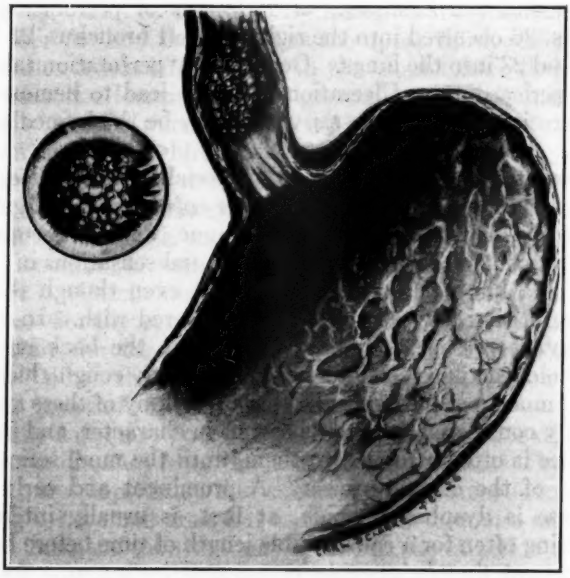


FIG. 1.—A small carcinomatous ulcer in lower end of esophagus. (Esophagoscopic picture in insert.)

esophagus, however, revealed an eroded area in the lower third. The stomach on Roentgen ray examination presented no abnormalities. The patient continued to lose in weight and strength, the cough and hoarseness continuing on uninterruptedly notwithstanding all forms of medication. He died without manifesting any signs of dysphagia or pain. At autopsy a large ulcerating carcinoma of the lower third of the esophagus was found, presenting but a very slight constriction above the lesion.

Hoarseness which is ordinarily a late manifestation, when present becomes often extremely persistent. It is due to a recurrent nerve paralysis, or to the irritation of the secretions produced by the growth. The paralysis of the vocal cord is usually unilateral.

The difficulty in deglutition, which at first is only slight and temporary, becomes severe and progressive. It is at first only noted in swallowing solids, which may require large amounts of water to aid in this process. After a short time, as the obstruction becomes more marked, even liquids are swallowed with increasing difficulty until finally nothing can be taken. The difficulty in swallowing is more marked at certain times than at others, inasmuch as the bolus of food may be too large to pass through the obstructed lumen due to inadequate mastication. At times the patient may be able to force the contents into the stomach by swallowing and pressure movements. Sooner or later the pain becomes more intense and regurgitation of food occurs. A history of regurgitation of food occurred in 83 of our cases (65 per cent). In the later stages of the disease as the growth enlarges, dilatation of the esophagus above the mass becomes more extensive, the largest forms of dilatation being associated with those obstructions situated in the lower third of the esophagus. The dilatation may retain large quantities of contents for a considerable period of time, which may lead to the erroneous impression that food is being retained in the stomach; but the contents are sooner or later regurgitated and are characterized by a foul-smelling odor. They contain undigested, decomposed food mixed with mucus and at times with fragments of the tumor mass, together with the bloody and purulent detritus. At this period, the constitutional signs of cancer become evident. The patient is troubled with a profuse secretion of saliva, loses flesh and strength, and becomes anemic and cachectic, due in part to his inability to partake of sufficient nourishment as well as to the toxic effect produced by absorption from the growth.

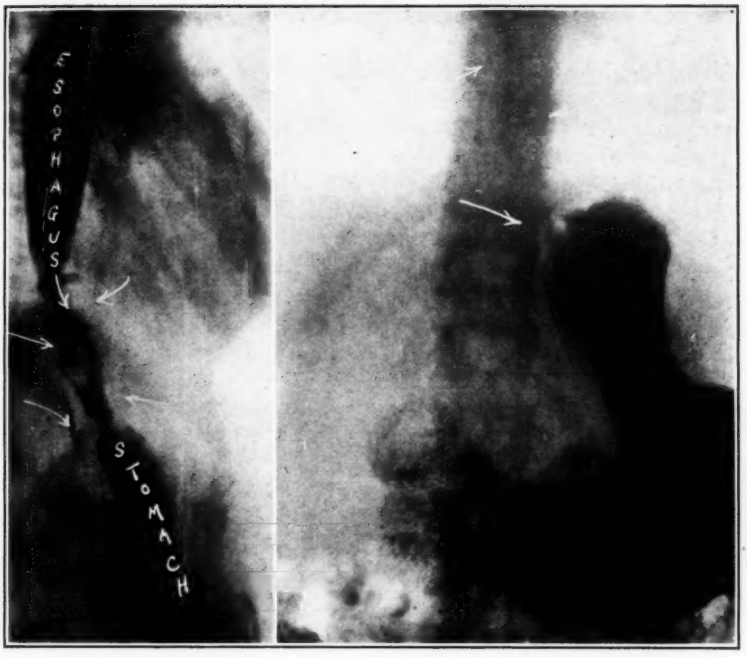
As the disease progresses extensive invasion into the surrounding structures either directly or through metastases takes place with interference of the function of the lungs, producing dyspnea or recurrent laryngeal paralysis, occasioning hoarseness, or perforation may occur into the large air passages, mediastinum or into neighboring bloodvessels, or involvement of the spine may eventuate in symptoms of spinal-cord disease.

Diagnosis. In the diagnosis of esophageal cancer the clinical history of this affection must be taken into account, which is usually rather suggestive. Whenever a patient of over forty years of age and especially of the male sex, who has previously been entirely free of any digestive disturbance, complains of the slightest difficulty in deglutition the possibility of this affection should be considered and further investigations instituted. The second deglutition murmur of Meltzer, which usually is heard over the sternum within twelve seconds may be delayed, due to obstruction to fifty to sixty seconds, or may even be entirely absent. Palpation of the cervical, axillary or supraclavicular glands may reveal some thickening or enlargements.

Not many years ago great emphasis was placed upon the diagnostic information obtained by means of the application of bougies, with the suggestion that with the difficulty encountered in the passage of this instrument, together with the evidence afforded by the presence of blood-stained mucus noted on its withdrawal, the question of malignancy could be definitely determined. While the blind passage of the bougie, under careful manipulation, often gives

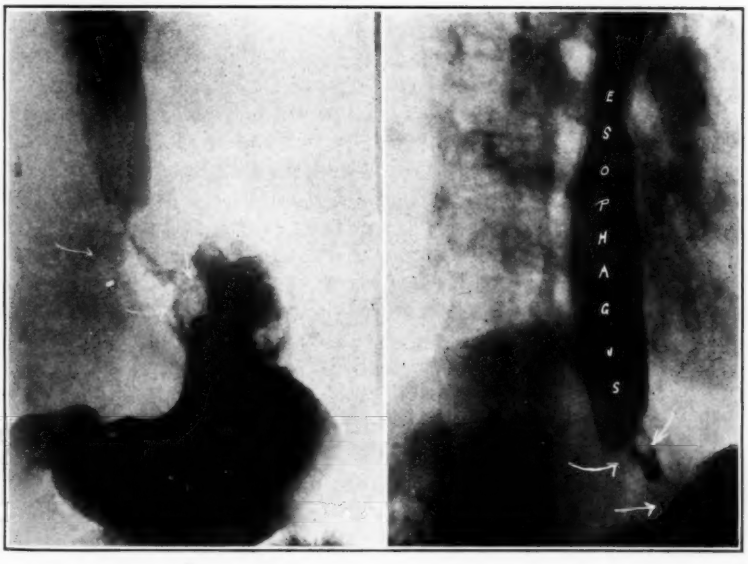
FIG. 2.—Perforated carcinoma of the esophagus.

reliable information and its use is only occasionally followed by accidents, Waggett[19] calls attention to the fact that this procedure is attended, however, with considerable danger and should never be practised. The cautious application, however, of a blunt olive guided through a thread previously anchored in the intestine may be undertaken with but slight risk and may be helpful in diagnosis (Fig. 2).



A *B*

FIG. 3.—*A*, Roentgenogram showing the lower end of the esophagus and stomach. No irregularities or obstruction noted. *B*, Six weeks later, note marked carcinomatous involvement with obstruction in lower end of esophagus.



B *A*

FIG. 4.—*B*, Roentgenogram showing carcinoma of lower end of esophagus, also involving portion of the cardia of the stomach. *A*, shows an esophagus with marked obstruction due to carcinoma in the lower end.

The danger in the application of bougies is illustrated by a case reported by us. A woman, aged thirty-one years, had had definite indications of carcinoma of the esophagus, together with a very marked stricture. A gastrostomy was performed and a small olive passed from below up and the stricture dilated; something was felt to give away by the operator. A few days later marked dyspnea with temperature set in and a pyopneumothorax was discovered in the left chest, from which a quart of brownish pus was aspirated. The following day resection of a rib was performed and a large quantity of foul-smelling pus evacuated. On the next morning the patient died. At autopsy a perforation was noted in the cancerous mass.

However, the recognition of early carcinoma of the esophagus can only be obtained by means of one or by both of two methods of examination, that is, by the use of the Roentgen ray and esophagoscopy.

By means of the Roentgen ray the seat of the obstruction may be determined as well as its degree, the extent of the growth, length of the stricture, character of dilatation above and surrounding involvement. The fluoroscope offers an ideal method for the examination of esophageal conditions. The meal can be visualized as it descends the esophagus, and the slightest irregularity of the lumen may be noted in the early cases, while tortuosity involving a considerable portion of the esophagus with stricture may be detected in the latter stages of the disease. With films certain of these findings can be preserved for further study. In all instances fluoroscopy should precede esophagoscopy. In the routine Roentgen ray examination of the gastrointestinal tract it is frequently possible to arrive at an early diagnosis of this affection. For the esophageal investigation, the patient is placed in an oblique or lateral position in order to expose the esophagus to view. An ordinary opaque meal is essential and must be viewed under the fluoroscope as it descends down the esophagus into the stomach. Under normal conditions the passage is rapid. Following this procedure, a thick, breaded, pasty meal is swallowed which descends slower and by means of which a far better detail of the lumen can be ascertained. In the early cases, obstruction being absent, the ordinary liquid meal passes through the esophagus so rapidly, that a small lesion is usually overlooked. By means of the thicker meal, however, the lesion can usually be determined under the fluoroscope. In fact, films at this stage are usually unsatisfactory. The first Roentgen ray sign of early carcinoma is a slight irregularity in the lumen of the esophagus, which however, does not produce any delay in the passage of the meal. It is not uncommon for the patient to complain of a distress or discomfort at this area and slight pain may be produced as the meal passes over the lesion. These signs are of great significance and can only be ascertained by means of fluoroscopic examinations. In one

of our cases, a man aged fifty-six years, the Roentgen ray revealed a slight irregularity in the lumen of the esophagus at the level of the fifth dorsal vertebra; no obstructive signs were revealed. The meal passed down rapidly. Slight pain was, however, manifested as the meal passed over the irregular area. A diagnosis of carcinoma of the esophagus was made which was later confirmed by an esophagoscopic study.

But even the Roentgen ray signs may be rendered uncertain by other conditions which may mask the actual disease. Thus Sauermondt reports a case of stenosis of the esophagus at a distance of 18 cm., thought to be due to spasm, but which was actually produced by a carcinoma located at 24 cm.

In advanced cases, the disease presents the appearance of an irregular or moth-eaten area and the lumen of the esophagus is more or less encroached upon by the growth, a stricture being produced with a slight degree of dilatation above the tumor.

Roentgen ray examinations were made in 116 of our 128 cases. By means of fluoroscopy lesions were observed consisting of but slight irregularities in the lumen of the esophagus, while in others large moth-eaten areas were noted with stricture and more or less dilatation of the esophagus above the lesion. According to our experience, the dilatation of the esophagus in cancer is not so extensive as is observed following cardiospasm.

The esophagoscope, however, presents the most direct and positive evidence regarding this affection, and under skilled hands may be introduced without danger and with but slight discomfort to the patient. Its use should always be preceded by fluoroscopy. Accidents, however, do occur with the use of this instrument due to laceration and penetration of diseased tissue, or to an attempt to pass through the stricture. It is never necessary to pass closer to the stricture than 2.5 cm., a distance from which the diseased area can be cleansed with cotton swabs, or by means of an aspirating tube, fragments removed with forceps or dilatation of the stricture accomplished. In utilizing the esophagoscope, the progress of the instrument should be directed with gentle pressure and the lumen of the esophagus always kept under the direct vision of the operator.

In 2 instances of carcinoma of the esophagus which have come under our observation and which were reported by us, perforation was produced by the esophagoscope. In the first instance, the perforation occurred into the right lung with the production of pneumonia and abscess, and in the second, into the right lower bronchus, which was followed by bronchopneumonia and a rapid fatality. However, with reasonable care, accidents of this character can be avoided. The advantage of esophagoscopy, over all other methods of investigation, is that while the information obtained from the latter is dependent largely upon the degree of obstruction present, this form of examination, on the other hand, visualizes the esophagus and the lesion itself before obstruction has been produced and,

at the same time, presents an opportunity of removing a portion of the growth for microscopic examination. Thus, malignant ulcerations, masses and granulations can be directly and accurately localized and the appearance noted. The growth may be early and limited in area or may be large, extending over a comparatively large area of the esophagus, or may encircle it. There is frequently present a condition resembling leukoplakia as an accompaniment of early cancer. The infiltrated part of the wall may project into the lumen, producing a crescentic polypoid or cauliflower appearance. The wall is ordinarily smooth, however, and often very red, though occasionally it is pale. The surface frequently ulcerates and takes on a nodular or granular appearance. In advanced cases, the entire circumference may become involved, producing an annular constriction or even a funnel-shaped stenosis.

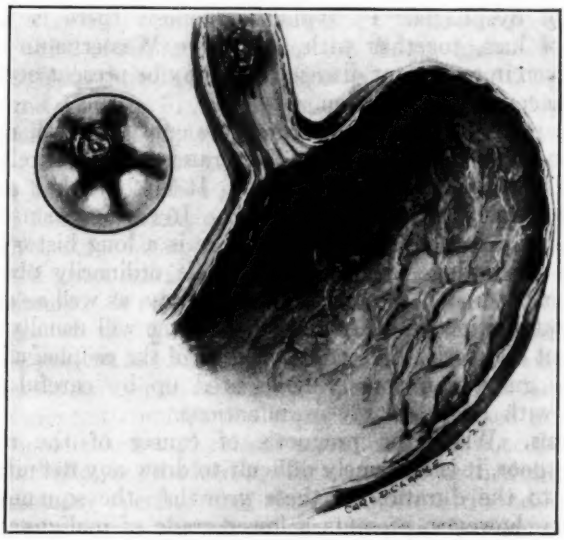


FIG. 5.—Small cauliflower carcinomatous growth in lower end of esophagus. (Esophagoscopic picture in insert.)

Jackson[11] notes the following appearances as indicative of early cancer of the esophagus.

"1. Absence of one or more of the normal radial creases between the folds.

"2. Asymmetry of the inspiratory enlargement of the lumen.

"3. Sensation of hardness of the wall on palpation with the tube.

"4. The involved wall will not readily be made to wrinkle when pushed upon with the tube mouth."

In the later stages, the following characteristics have been especially emphasized by Jackson: The ease with which the esophageal wall bleeds, and the sensation of rigidity of the part involved

when palpated with the esophagoscope, and finally the absence of dilatation above the lesion except in the very late stages of the disease.

Esophagoscopies were performed in 62 of our 128 cases. The findings were much like those described above.

Differential Diagnosis. In the diagnosis of carcinoma of the esophagus, the following affections must especially be taken into consideration: Benign strictures, as those produced by the swallowing of caustics; syphilitic strictures; simple ulcerations, producing stricture; cardiospasm with idopathic dilatation of the esophagus, and affections without the esophagus pressing upon the gullet, such as aneurysms, mediastinal tumors, or affections of the spine.

In benign stricture of the esophagus the patient ordinarily presents a history of the swallowing of some caustic substance; this affection usually occurs in young individuals, and there is frequently a long history of dysphagia. In syphilitic stenosis there is usually a history of lues, together with a positive Wassermann reaction, though even in malignant disease there may be present occasionally a simultaneous luetic infection.

Simple peptic ulcer may, at times, be confused with malignant ulceration. The esophagoscopic appearance is not entirely characteristic, though according to Jackson. It is somewhat similar to the gastroscopic picture of gastric ulcer. In cardiospasm with idiopathic dilatation of the esophagus, there is a long history of difficulty in swallowing, and the affection is ordinarily observed in younger individuals. A careful Roentgen ray, as well as esophagoscopic examination, in all of these conditions will usually point to the correct diagnosis. Affections outside of the esophagus pressing upon the gullet can usually be cleared up by careful physical, together with Roentgen ray examinations.

Prognosis. While the prognosis of cancer of the esophagus is always poor, it is extremely difficult to draw any definite conclusions as to the duration of these growths; the squamous-celled carcinoma, however, presents a lower grade of malignancy. The duration of symptoms in general, according to Turner, may extend from three weeks to nine months; the average being four and a half months, though it is not uncommon to observe cases, according to our experience, covering a period of from a year to a year and a half, or even two years. Starlinger[20] presents the following table indicating the duration of symptoms in his 132 cases from their first appearance until death:

TABLE V.—DURATION OF NOTICEABLE SYMPTOMS (STARLINGER).

	Per cent.
Under one month	0
1 to 3 months	20.5
3 to 6 months	35.3
6 to 9 months	23.0
9 to 12 months	10.2
Over 12 months	11.0

Death usually occurs due to inanition, cachexia or to perforation, especially into the respiratory organs producing pneumonia, abscess of the lung, pleurisy or pneumothorax, or into the pericardium producing pericarditis, or pneumopericardium; or to hemorrhage due to ulceration of large bloodvessels.

Treatment. As soon as the diagnosis of cancer of the esophagus is established, the question of surgical interference must at once be considered. Unfortunately, the danger attending radical removal of these growths is so great that this procedure cannot by any means be urged upon patients. A few successful instances of removal have, however, been reported by Turner[8] and by Wallace[21] from the upper third of the esophagus; and one by Torek,[22] and one by Eggers[23] from the middle third. Torek's patient lived more than twelve years, and the case of Eggers was in good health after a year. The cases reported by others as Bengolea,[24] Meyer[25] and Lilienthal,[26] however, were only temporarily benefited. Successful resections of the lower third of the esophagus for this disease have been reported by Torek[22] from the clinics of Voelcker, Kummell and Zaaijer[27] Hedblom,[28] and William J. Mayo[29] had successes in single instances. The technique of this operation has now been sufficiently perfected, that the procedure must at least be considered whenever the diagnosis has been established sufficiently early. According to Torek, far fewer failures would occur if the patient were admitted at a much earlier stage for operation. The operation, in our experience, from which great relief can be obtained in cancer of the esophagus is gastrostomy. It should, however, not be deferred until the very late stages of the disease. When performed moderately early before the patient has been too greatly weakened and exhausted by the disease, it may be accomplished with but slight risk, and at times with the greatest comfort to the patient. If deemed advisable, it may be undertaken under local anesthesia. It not uncommonly occurs that following the feedings for a certain length of time through the gastrostomy opening, that the congestion surrounding the carcinomatous stricture may disappear, allowing the patient to again partake of soft nourishment swallowed through the normal route for some time without difficulty. In addition, the very distressing death from starvation can be prevented by this procedure. While the operation may not prolong life, our experience is not in accord with that of Vinson,[9] for it has afforded much relief, as well as comfort to many of our patients, even though this may have been but temporary.

In the further treatment of this disease, dilatation of the carcinomatous stricture with olive bougies of graduated size as recommended by Vinson, even though passed over a thread as a guide, is a procedure, according to our experience, of doubtful utility, and at the same time is rather hazardous. Radium and the Roent-

gen ray treatment have afforded but slight temporary relief in a number of our cases, though isolated cures have been reported. Guisez[10] has recently reported 6 cases of cancer of the esophagus in which cures were effected by means of radium, and Yankhauer[30] points to the relief afforded particularly in swallowing following its use. Stone[31] has called attention to the fact that radium but rarely effects a cure and actually adds a certain degree of risk, due to the possibility of the production of perforation when the lesion is overdosed.

As a further means of relief, the local application of cocain and the administration of opiates may be recommended.

The diet should be carefully regulated in this disease, so as not, as far as it is possible, to produce any irritation of the diseased or stenosed esophagus. Solids should, therefore, be avoided. Milk is best borne. It can be rendered more nutritious by the addition of cream, eggs, malted milk. In addition broths of all kinds, cocoa and buttermilk may be given. At times it may become necessary to resort to rectal feeding.

Conclusions. 1. Carcinoma of the esophagus is not an uncommon affection, occurring, however, less frequently than cancer of the stomach. It is far more often observed in males, occurring in about the proportion of 5 males to 1 female.

2. This disease is more apt to affect those sites which present physiologic narrowing of the lumen due to the greater irritation produced by the passage of food at these areas, that is, the entrance of esophagus, the aortic, bronchial and diaphragmatic constrictions.

3. The squamous-celled epithelioma and adenocarcinoma are the most common varieties of growths, representing 90 per cent of tumors of this region.

4. The early symptomatology is indefinite and the premonitory signs vague and inconstant. The patient frequently complains at first only of unusual sensations in swallowing and of a lump rising into the throat. A prominent and early sign is dysphagia, and regurgitation of small amounts of blood may be observed occasionally at this stage and later of food. The recognition of early carcinoma of the esophagus can be best accomplished by means of the Roentgen ray and esophagoscopy.

5. The danger attending radical removal of the growth is so great that this procedure cannot be urged upon patients even though a few successful instances of removal have been reported. Considerable, though only temporary, relief may be obtained by means of gastrostomy, if not performed too late. The dilatation of the carcinomatous stricture by means of bougies as recommended by Vinson and the use of radium are procedures which, according to our experience, are of doubtful utility.

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THE TREATMENT OF ARTHRITIS WITH SALTS OF O–IODOXY–BENZOIC ACID.

By James E. Cottrell, M.D.,

PHILADELPHIA.

(From the Medical Clinic of the Hospital of the University of Pennsylvania.)

The three iodin substitution products of benzoic acid have been known to chemists since 1892. The one with which we are concerned, o-iodoxy-benzoic acid, corresponds to the formula illustrated, containing two double-bonded oxygen atoms linked to the iodin

(Fig. 1). When pure, it is a white powder which turns reddish-brown on exposure to light, difficultly soluble in warm water; the dry substance explodes when heated, giving off purple fumes and an odor of iodin. It is a fairly strong acid; its most striking chemical characteristic is its property of acting as an oxidizing agent. The sodium and ammonium salts are readily soluble in water. The iodin content of the ammonium salt is between 40 and 45 per cent.

Loevenhart and Grove,[1] in 1911, described improved methods of preparation of o-iodoxy-benzoic acid, and studied its physiologic action. A summary of their results is as follows: O-iodoxy-benzoic acid is a physiologic oxidizing agent, inasmuch as it can furnish oxygen for the peroxidase reaction of blood. When administered intravenously, it is not hemolytic. It depresses the vasomotor center, causing a fall in blood pressure; it also depresses the respiratory center and causes a period of apnea in repose, with spontaneous resumption of respiration.

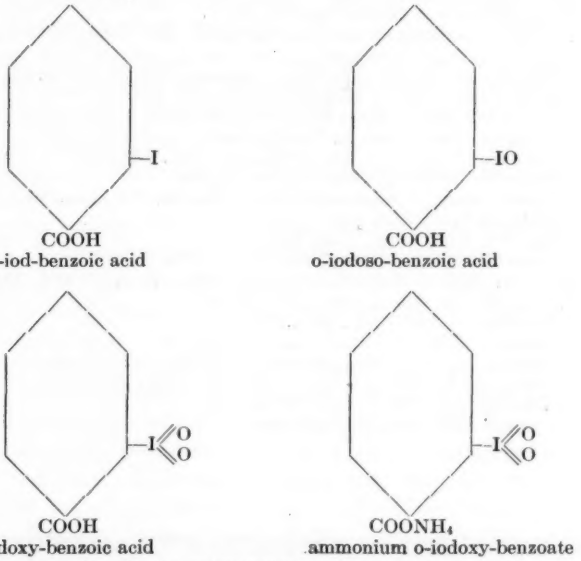

FIG. 1.—Formulæ of iodin substitution-products of benzoic acid.

Other rather extensive studies were made about the same time. Arkin[2] found that sodium o-iodoxy-benzoate exhibits marked bactericidal action, though less effective against staphylococci than against Bacillus typhosus, Bacillus coli, or Bacillus pyocyaneus. He found it to be quite as active in blood serum as in water. Arkin and Fink[3] found it to have no constant effect on the catalase value of blood and tissues. Amberg and Knox[4] found that the local inflammatory process in an allergic reaction (the reaction to intracutaneous injection of serum in sensitized dogs and rabbits) is

diminished by the intravenous injection of sodium o-iodoxy-benzoate, whereas a systemic allergic reaction is unaffected. Hektoen[5] found that intravenous injection of sodium o-iodoxy-benzoate in dogs stimulates the production of antibodies. Young and Youmans[6] state that the toxicity of sodium o-iodoxy-benzoate is dependent more on the rate of injection than on the dose administered. All of these investigators agree that the properties of o-iodoxy-benzoic acid are due to the presence of oxygen in the molecule, for o-iodbenzoic acid, which contains no oxygen, has not such properties, whereas they are shared to some extent by o-iodoso-benzoic acid, which contains one oxygen atom less than o-iodoxy-benzoic acid.

The systematic use of o-iodoxy-benzoic acid in the treatment of arthritis, under controlled conditions, was initiated by Young and Youmans[6, 7] of the University of Michigan. Their series, reported in 1926, comprised 43 patients, ranging in age from the second to the seventh decade; 24 were male and 19 female. All but 4 of their cases were considered to be chronic, and included examples of hypertrophic and atrophic forms, as well as gonococcal arthritis. The duration of the disease in the chronic cases varies from less than a year to more than ten years. Their patients each received from 6 to 25 injections of the drug, in "courses" of about 6 injections, at intervals of three or four days, with a lapse of usually six weeks between courses in those instances where more than one course was given. Of their 43 cases, 56 per cent were said to be markedly improved; 23 per cent moderately improved; 14 per cent slightly improved; and 7 per cent unimproved.

Smith,[8] of the Boston City Hospital, has reported a series of 33 patients, treated with the drug in a similar manner. Two of his cases were classed as "arthralgia," 12 as acute arthritis, 16 as chronic arthritis, 2 as gonococcal arthritis, and 1 as acute rheumatic fever. All but 3 of his patients showed improvement, as evidenced by diminution of pain or of swelling, or by improvement in function.

The use of o-iodoxy-benzoic acid in the treatment of arthritis, especially infectious arthritis, is based upon its germicidal power for streptococci and staphylococci, and upon its power of stimulating bodily defense mechanisms in general. It seems reasonable to suppose that this nonspecific stimulation of reactive processes might also be effective in noninfectious forms, if we agree with many students of the subject that some arthritides are noninfectious. Since Pemberton and his associates[9] have shown that in many arthritics there is increased oxygen saturation of venous blood and hence presumably decreased removal of oxygen in passage through the capillaries, an obvious possibility is that the power of o-iodoxy-benzoic acid to act as a physiologic oxidizing agent is a factor in the results. A natural explanation for the analgesic effect of the drug, often very striking, may be seen in the similarity of its chemical structure to that of the salicylates, though it is seldom permissible

to base deductions as to physiologic action on superficial resemblance in chemical formulæ.

In the spring of 1926, Dr. A. G. Young sent to us, in the Medical Division of the Hospital of the University of Pennsylvania, a supply of the drug, and we have used it in the treatment of a small series of cases, most of them in the University Hospital and the Episcopal Hospital. The series comprises 21 cases. The majority of the patients presented long-standing or very severe arthritis; in almost all, other forms of treatment had been used with little or no improvement. In general, they were cases of such nature as to constitute a severe test of any therapeutic procedure. Seven were male and 14 female. The youngest was twenty-three and the oldest seventy years of age. The proportion of the various types of arthritis, and the average duration in each group, are shown in Table I.

TABLE I.—TYPES OF ARTHRITIS.

Type.	Number of cases.	Per cent.	Average duration.
Acute infectious	2	9.5	1.5 mo.
Subacute infectious	3	14.3	1.0 mo.
Chronic infectious (arthritis deformans)	13	61.8	4.2 yrs.
Gonococcal	3	14.3	1.0 wk.

In the 13 cases classed as "chronic infectious," the duration of the disease varied from eight months to over ten years, and the age of the patients from twenty-three to seventy years. These patients presented typical chronic arthritis with varying degrees of crippling and deformity, belonging to the group of "proliferative" arthritis, although the history of 1 case suggests somewhat the "menopause arthritis" described by Cecil and his associates.[10, 11] Several of the patients are still under observation or treatment. Examples of almost every conceivable treatment of arthritis are to be found in the history of the group prior to the administration of o-iodoxy-benzoic acid, including measures for the eradication of infectious foci, injections of foreign protein (Coley's fluid, milk-proteins, bacterial vaccines), physiotherapy, orthopedic treatment, light, radioactive water, and the whole gamut of antiarthritic drugs.

It is not the purpose of this report to enter into a discussion of the classification and etiology of chronic arthritis in general, but we have considered all these cases as infectious. It seems extremely difficult, in any given case, entirely to eliminate the possibility, or even the probability, of origin from some focus of infection. In all but one of the chronic cases reasonably definite foci were present when the patients came under our care, or they had had operative procedures for the eradication of foci previously. In one acute case, although its infectious nature would be granted by all, no focus was demonstrable. Tuberculous and syphilitic arthritides, and acute rheumatic fever, are not represented in the group. The number of times various common sites of foci were implicated is

represented in Table II. The number of instances of tonsillar infection may perhaps be taken with some reservations, but at least in that many cases someone considered the tonsils sufficiently suspicious to recommend their removal.

TABLE II.—INFECTIOUS FOCI.

Tonsils	14	
Teeth	7	
Sinuses	3	In various combinations (21 patients)
Genito-urinary (non-venereal)	3	
Genito-urinary (venereal)	3	
Gall bladder	1	

In all cases, we began by instituting a careful search for foci, investigating routinely the teeth, tonsils, sinuses, ears, the prostate in men, the pelvic organs in women, by clinical, bacteriologic and roentgenologic methods. Where infectious foci were found, they were treated appropriately; and in the earlier cases in the series, time allowed to elapse before beginning treatment with the drug, to evaluate beneficial results which might be obtained merely from the clearing up of focal infection. Following the suggestion of Barrow and Armstrong,[12] the stools of several patients were carefully examined for parasitic protozoa by Dr. Frank B. Lynch, of the Pepper Laboratory of Clinical Medicine, with, however, negative results in each instance. In chronic cases with any impairment of function, physiotherapy was started promptly and continued throughout the course of treatment, consisting of baking, massage, passive movement, and exercise. The usefulness of such measures, properly applied, can scarcely be overemphasized. Orthopedic measures for the correction of deformities or the relief of pain were used when indicated. In general, other drugs were avoided while using o-iodoxy-benzoic acid, except when rarely an analgesic was needed. Salicylates are especially to be avoided, as it is stated that they increase the severity of reactions.

Intravenous injection is by all means the method of choice in administering the drug, and for this the ammonium salt is used. The standard dosage of ammonium o-iodoxy-benzoate is 1 gm. dissolved in 100 cc. of sterile distilled water, given approximately twice weekly. It is injected by the gravity method, and must be given slowly, allowing ten to twenty minutes for 100 cc. to run in. Rapid administration tends to produce severe reactions. Usually during the injection the patient experiences a curious burning and smarting of the eyes, tongue, mouth, nostrils, and sometimes of the general body surface; this subsides in a few moments. Almost invariably there is a more or less pronounced reaction after the injection; it may come on within half an hour, or it may be postponed for three or four hours. Most often it consists only of slight malaise and perhaps little nausea. Severe reactions are marked by a chill, vomiting, and purging. Very rarely do the patients find the reac-

tions sufficiently uncomfortable to cause them to object to the use of the drug. There is sometimes a rise in temperature of from 1° to 5° F.; more often there is no rise. There seems to be no rule as to the type of cases in which severe reactions occur, and no relation between the degree of the reaction and relief obtained; nor is the reaction at all uniform with successive doses in a given case. In general, more severe reactions were met early in the study of this series, when we were using the ammonium salt extemporaneously prepared by neutralizing a solution or suspension of the free acid with strong ammonium hydroxide; it is to be suspected that chemical impurities aggravated the reactions. Since we have been using the pure, stable ammonium salt, which needs only to be dissolved in the requisite amount of sterile distilled water, the reactions have been far less pronounced. We have never seen clinically the apnea and fall in blood pressure which are described in laboratory animals.

The mechanism of the reaction is uncertain. Certain features would indicate that it differs from the mechanism of protein shock. There is not the preliminary suppression of polymorphonuclear leukocytes with a secondary rise; in fact, there does not seem to be any constant effect in the leukocyte count, although it is stated[1] that the drug produces a polymorphonuclear leukocytosis. In one patient to whom the drug was administered by mouth a reaction was produced by each dose, less marked than after intravenous injection, but similar in kind. This production of a reaction after absorption from the gastrointestinal tract as well as after parenteral administration argues dissimilarity to the mechanism of protein shock.

For patients with whom great difficulty is experienced in intravenous injection, the drug may be given by mouth or by rectum. For oral administration, calcium o-iodoxy-benzoate is preferable to the ammonium salt, as it seems to produce less gastric irritation. A larger dose, usually 1.5 gm., is given in capsules of 0.5 gm. each during a few hours, the patient preferably fasting or eating very lightly before the administration of the drug. The dose is repeated approximately twice a week. Slight nausea is sometimes induced, rarely vomiting, and very rarely (one patient only in this group) any other reaction. For rectal administration the dose is 1 or 1.5 gm. of ammonium o-iodoxy-benzoate in 2 per cent solution, given after a cleansing enema; reaction of any kind is unusual, and the drug is usually retained. The therapeutic effect from oral and rectal administration is probably always less marked than from intravenous administration, but the chance of benefit is sufficient to make oral or rectal administration worth while if intravenous injection is impracticable. But it must be emphasized that the intravenous route offers the best chance for satisfactory results, and that oral or rectal administration should be resorted to only if intravenous injection is quite impracticable, or as a supplement to intravenous treatment.

The drug is best given in "courses" of 6 or 8 doses at semiweekly intervals, with a rest of three to six weeks between courses. One patient in this group has received 3 courses totaling 20 injections. Others have received from 3 to 17 doses. All but 3 have received at least part of their treatment intravenously.

The criteria by which improvement has been judged are diminution in pain and swelling, subjective sense of greater freedom of motion, actual objective improvement in joint function, and increase in the patient's sense of general well-being. Improvement in cases of chronic arthritis is obviously a relative matter; if a patient who has been bedfast is enabled to walk by means of braces and crutches, his state is considerably improved, even though he still be badly crippled. The condition of many of the patients in this group was such that to obtain any improvement at all constituted a therapeutic triumph. All but 3 of 21 patients have shown improvement of varying degree. Relief of pain is often prompt and marked, especially in acute and subacute cases; some patients complain of a preliminary increase in pain for a few hours after an injection. In the great majority of chronic cases with crippling, there has been improvement of function, from slight to very marked. Some patients who were unable to close the hands, or to get the hands to the head, or to rise without assistance, were able, after treatment, to perform those movements. Two patients who had had especially varied and intensive previous treatment both said that this drug was the first thing that had ever benefited them. There are often recurrences of symptoms during the intervals without the drug, but in a case of chronic arthritis the treatment must of necessity be very prolonged. In some cases, after satisfactory improvement at first, we seemed to reach a point after which further improvement did not occur; in at least one the onward progress of the disease seemed not to have been stopped in spite of initial improvement. Table III shows a summary of the therapeutic results in the whole series, and Table IV the therapeutic results in reference to the types of arthritis.

TABLE III.—SUMMARY OF RESULTS.

	Number.	Per cent.
Cured	2	9.5
Markedly improved	6	28.6
Moderately improved	4	19.0
Slightly improved	6	28.6
Unimproved	3	14.3

TABLE IV.—RESULTS IN REFERENCE TO TYPES OF ARTHRITIS.

Type of arthritis.	Cured.	Markedly improved	Moderately improved	Slightly improved	Unimproved	Total.
Acute infectious	..	..	2	..	..	2
Subacute infectious	2	..	1	..	..	3
Chronic infectious	..	4	1	5	3	13
Gonococcal	..	2	..	1	..	3

We have seen no ill effects of serious importance. Some of the reactions have been severe, but not alarming; most patients do not even find them seriously annoying. In one case, not included in this series, the reaction to the first injection was severe enough to cause the patient to refuse other treatment. Venous thrombosis occurs at times; its incidence is minimized by careful technique in the injection, and by following the ammonium o-iodoxy-benzoate solution with a little physiologic saline solution to wash out the vein. If some of the o-iodoxy-benzoate solution escapes into the subcutaneous tissues it is only mildly irritant. The fear has been expressed that on account of the high iodin content of ammonium o-iodoxy-benzoate (between 40 and 45 per cent), hyperthyroidism might be induced. But in that combination the iodin is presumably physiologically inert, and the combination is probably not broken down at all in the body. Young[13] states that practically all of the iodin injected as ammonium o-iodoxy-benzoate can be recovered in the urine still in the same combination; that is, as o-iod-benzoates, or as iodin substitution products of hippuric acid. We have not seen any such case of induced hyperthyroidism.

Report of Cases. CASE I.—M. G., female, aged twenty-seven years (University Hospital). Onset of the disease was about three years previously, with gradual progressive involvement of all the large joints, the fingers, and the spine. She had had tonsillectomy two years, and thyroidectomy one year, before admission. Roentgenogram showed atrophic joint changes. No active foci were found.

The hands could not be clenched. The wrists were limited in flexion and extension. The limit of extension of the elbows was about 165 degrees. There was marked crepitation in both knees, but passive extension to practically normal range was possible. The hips could be flexed to 90 degrees; the spine was held rigidly.

She received 17 injections in 3 courses. After the first course, she felt greatly improved. She could close both hands, though not tightly; both elbows were extensible to about 170 or 175 degrees, and there was practically no limitation of motion of the knees or hips. She still walked with a limping, shuffling gait.

In the intervals between courses, there was some increase in pain, but no relapse so far as function was concerned. From the second and third courses she received considerable relief of pain, but little if any further improvement in function. She received physiotherapy throughout the treatment.

CASE II.—Mrs. G., aged seventy years, private patient of Dr. David Riesman. For about five years she had had pain, stiffness, and loss of motion in various joints, most marked in the knees, affecting also the fingers, jaw, wrists, hips, and shoulders. The tonsils had been removed; careful search showed no other foci. She had received very extensive and varied treatment.

The knees were swollen. There were atrophy and spindle deformity of the fingers, and swelling of the right wrist. Other joints showed no objective changes.

She received 3 courses totalling 20 injections, with a sharp reaction each time. There was marked improvement, especially in the swelling about the knees, and in the function of knees and fingers. She stated that she was better than she had been in years.

CASE III.—A. S. G., female, aged fifty-four years (University Hospital). Onset was three years previously, with swelling and stiffness (at first painless) of the right knee; a year later, the middle finger of the right hand became involved. Two months before admission, the left knee, all joints of both hands, and the left shoulder were affected, with a great deal of pain. She apparently had an attack of cystitis about six weeks before admission. She had been confined to bed for about two months.

There was spindle deformity of all fingers; both wrists were swollen, and flexion and extension limited, but pronation and supination well retained. The elbows were very slightly limited in extension. The left shoulder was extremely painful, and abduction and circumduction almost impossible. There was effusion in both knees. She could not open her mouth fully.

The tonsils were found to be infected, and were removed under local anesthesia; severe shock resulted and almost proved fatal. She received baking and massage, and several colonic irrigations.

There were absolutely no veins available for injection, and she was given the drug by mouth. Really astonishing improvement ensued; after 3 doses she was entirely free from joint pain, said she felt better than she had for ten years, and insisted on going home against advice. The effusion in the knees was less in amount, but still present. Oral administration of the drug was continued at home for a time. At last reports, about three months later, she had maintained her improved condition without recurrence.

CASE IV.—P. C., male, aged twenty-seven years (University Hospital). Duration of the disease was about three and a half years. The left elbow was swollen and tender, and limited to about 150 degrees of extension. At the right shoulder, abduction was limited to about 75 degrees. Both knees were swollen and tender, and limited to about 160 degrees of extension. He was able to walk, but with some pain. The wrists had also been involved.

A tonsillar remnant was removed, and the left maxillary sinus drained surgically. Baking, massage, and ultraviolet radiation were employed. He received 7 intravenous injections of ammonium o-iodoxy-benzoate without any improvement.

CASE V.—N. B., colored, female, aged thirty years (Episcopal Hospital). Onset was a month before admission, with chills,

fever, sweats, and generalized joint pain, worst in the right knee and left shoulder.

The tonsils, obviously diseased, and several abscessed teeth were removed. There were some improvement under treatment with salicylates and injections of foreign protein, but joint pain and stiffness persisted. She was given 4 injections of ammonium o-iodoxy-benzoate; pain and stiffness completely disappeared after the first injection. She was discharged as cured.

CASE VI.—R. P., female, aged twenty-five years (Episcopal Hospital). Onset one week before admission, with severe fleeting pains in various joints and temperature of 103.5° F. The following day only the right ankle and the metacarpophalangeal joint of the left thumb were involved; those joints continued to be swollen, red, hot, tender, and extremely painful, disturbing sleep. She had had an appendectomy and oöphorectomy. Frequency of urination and burning were present; she had a profuse vaginal discharge; cervical smears were repeatedly positive for gonococci.

A plaster splint was applied to the ankle, and a gonococcus vaccine administered; the only local treatment of the gonorrhea was by vaginal douches. Some improvement resulted, but she continued to have pain most of the time. She was given 5 injections of ammonium o-iodoxy-benzoate; one of them, by mistake, consisted of 2 gm. instead of 1 gm., but there was no untoward results, except some gastric distress. After the first injection, pain in the ankle was markedly decreased, and movement caused very little discomfort; after the second, swelling and redness had subsided, and the splint was removed. After the third injection, gentle massage and passive movement were begun. After the fourth, she was able to be out of bed and had no pain. After the fifth, there was slight return of the pain during one night, but the patient insisted on leaving the hospital against advice.

Conclusion. This series is, of course, a small one, and it can only be said that results thus far are encouraging. Only further experience can determine the value of this drug. From present knowledge, we can say that certain cases of arthritis, of various types, are definitely benefited by treatment with the drug; that there are apparently no means of predicting which cases will, and which will not, be benefited; that it seems probable that the drug will prove to have a definite place in our therapeutic armamentarium against arthritis. Surely a drug which has given more than 80 per cent of improvement in various types of arthritis at least deserves a more extensive trial.

A brief scheme for the use of the salts of o-iodoxy-benzoic acid in the treatment of a patient follows:

1. A search for, and treatment of, foci of infection.

2. Administration of ammonium o-iodoxy-benzoate intravenously in doses of 1 gm. semiweekly for 6 or 8 doses. Subsequent courses may follow at intervals of three to six weeks, or longer. If intravenous injection is impossible, the drug may be administered by mouth (calcium salt) or by rectum (ammonium salt).

3. Concomitant and persistent use of physiotherapy in chronic cases.

4. Orthopedic treatment of deformities.

Lastly, the recollection that the drug is only one factor in the treatment—that these other resources must be used fully, and that in chronic cases the treatment may be persisted in for months or years.

The writer wishes to acknowledge his indebtedness to Dr. A. G. Young of the University of Michigan for many helpful suggestions, and for our original supply of the drug; to Dr. David Riesman, Dr. Joseph Sailer and Dr. Richard A. Kern, each of whom has allowed a private patient to be included in the series.

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THE EFFECT OF DISTENTION OF THE STOMACH AND COLON ON THE LOCATION OF CARDIAC DULLNESS.

By William A. Brams, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL,
AND
Robert A. Arens, M.D.,
CHICAGO, ILL.

(From the Departments of Medicine and Roentgenology. Michael Reese Hospital, Chicago, Ill.)

Our attention was drawn to the apparent displacement to the right of the left border of the cardiac dullness when either the stomach or colon was distended by gas. A search through the lit-

erature failed to reveal any satisfactory description or explanation of this apparent shifting to the right of the cardiac dullness as determined by percussion. We, therefore, attempted to reproduce these findings experimentally in order to draw some conclusions which could throw some light on the mechanism of this apparent displacement.

Ten patients with various types of normal chest were selected for these experiments. The right and left borders of the cardiac dullness, as well as the margins of the aortic dullness, were outlined by moderately heavy percussion and these outlines were marked by narrow strips of lead foil held in place by adhesive plaster. All percussion was performed with the patient in the standing position and with the chest about midway between inspiration and expiration. A Roentgen plate was then taken of the chest with the target 7 feet from the film while the patient held his breath in about the same degree of inspiration as when the heart was percussed. This first plate showed the relation of the cardiac dullness as percussed to the actual size of the heart and is illustrated by Fig. 1, *A* being the left and *B* the right borders. The patients were then given sodium bicarbonate and tartaric acid in solution and two or three minutes were allowed to pass in order to permit the formation of a considerable quantity of gas in the stomach. The cardiac dullness was again percussed and narrow strips of lead foil were placed along the outlines of the cardiac dullness. A distance plate was immediately taken with the patient in the same position as before and these films are illustrated by Fig. 2. The next step consisted of inflating the colon with air by means of a catheter to which an ordinary bulb was attached. The amount of air introduced into the colon was not measured but as much was given as the patient could stand. The cardiac dullness was again outlined and marked by lead foil as previously and another distance plate was immediately taken which was labeled Fig. 3. Particular care was taken to have the patient in the same position and respiratory phase during all percussion and while the Roentgen plates were being taken.

The results are best illustrated by a study of the plates which showed practically uniform results regardless of the shape of the chest. Since these experiments were performed on patients with normal stomachs, we cannot state whether similar results would be obtained in cases in which there is pyloric obstruction. We do not think, however, that there will be an actual displacement of the heart even in these cases as the inflated stomach was seen to rotate so that its greater curvature rose anteriorly while the lesser curvature turned posteriorly. The dilatation of the stomach occurred chiefly along the greater curvature and the resistance of the diaphragm would also have to be overcome before there could be any appreciable effect on the location of the heart. It is possible that

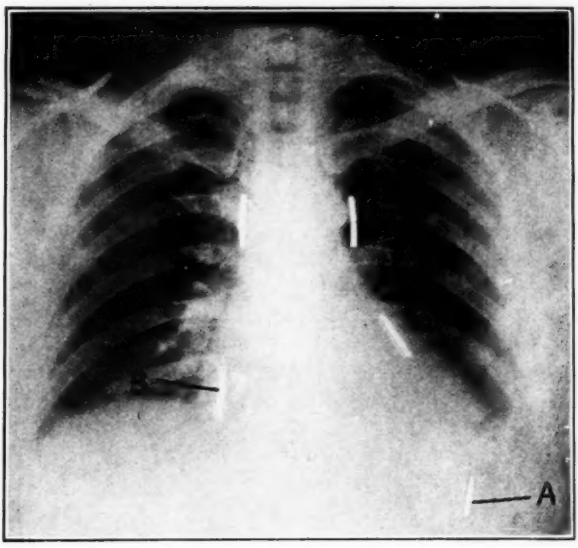

FIG. 1.—Distance plate in upright position. Cardiac outlines as obtained on percussion marked by strips of lead foil. *A*, is dullness at apex. *B*, dullness of right border.

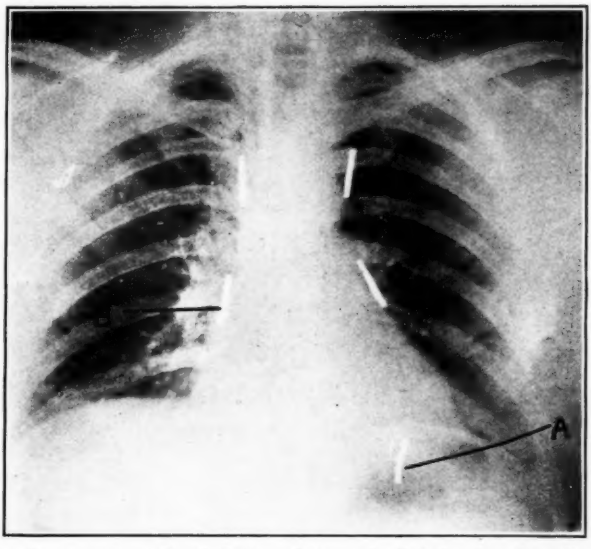

FIG. 2.—Same patient after inflation of stomach. Left border of cardiac dullness at *A* as obtained on percussion, well within actual location as seen on distance plate. Right border *B* remains unchanged.

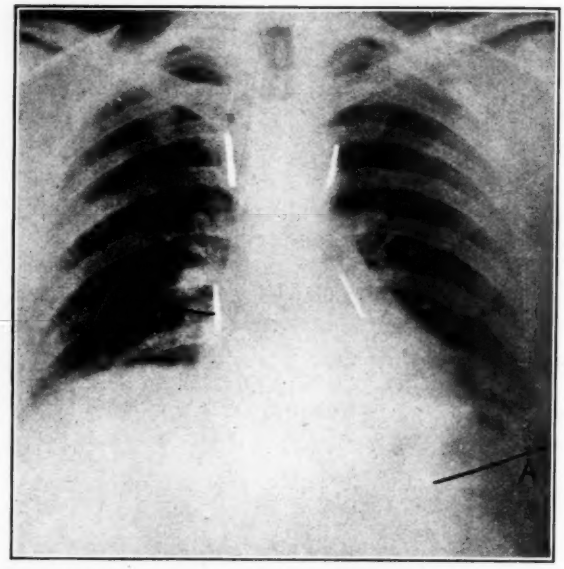

FIG. 3.—Same patient after inflation of colon. Results similar to those obtained on inflation of stomach but less marked.

some slight degree of shifting does occur but we were unable to determine this by comparing the films with one another. As previously stated Fig. 1 represents the control pictures of two different patients during ordinary respiration. The cardiac dullness, as outlined by the strips of lead foil, corresponds approximately to the actual outlines of the heart as shown by distance plates taken immediately after percussion. Fig. 2 represents the findings on percussion and on distance plates of the same patient after distention of the stomach by gas. It will be observed that the left border of the cardiac dullness, as outlined by percussion and as shown by the metal markers, is displaced to the right while the right border and boundaries of the aortic dullness remain approximately a sbefore. The displacement of the left border of the cardiac dullness, as compared with the actual position of the heart on the distance plates, amounted to from 1 to 1½ inches. It is evident that no actual displacement of the heart occurs and the apparent shifting is probably the result of transmission of a tympanitic element in the percussion note from the distended stomach. Similar results, but in a less marked degree, were obtained after inflation of the colon and the explanation is probably the same.

Résumé. 1. Distention of the stomach or colon can produce an apparent displacement to the right of the left border of the cardiac dullness as obtained by percussion.

2. This apparent shifting of the cardiac dullness is not associated with any actual displacement of the heart as determined by distance plates.

3. The apparent displacement on percussion may be explained by the transmission of a considerable tympanitic element in the percussion notes from the adjacent distended stomach or colon.

FURTHER OBSERVATIONS ON THE TREATMENT OF HAY FEVER WITH EPHEDRIN.*

By Fred W. Gaarde, M.D.,

and

Charles K. Maytum, M.D.,

division of medicine, mayo clinic, rochester, minn.

Various observers have studied the chemistry and pharmacology of ephedrin in association with its clinical value in different diseases.[1, 2, 3, 4, 6, 8, 9, 10] Cook, of the Department of Otolaryngology of Peking Union Medical College, first suggested local application

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of ephedrin, and Fetterolf and Sponsler investigated its effect on turgescent nasal mucous membrane. The latter found that there was shrinkage of the turbinates almost immediately, which persisted for almost three hours. The mucosa became paler, but never attained the ischemic pallor which follows the application of epinephrin, nor was there any local irritation or dilatation. They concluded that ephedrin had "all the advantages and perhaps none of the disadvantages" of epinephrin.

In 1925, we reported the results of the treatment of 26 patients suffering from autumnal hay fever.[7] Our conclusions at that time seemed to warrant the opinion that ephedrin afforded symptomatic relief to more than half the patients treated. Further observations were made during the season of 1926 with results similar to those of the previous season. In the season of 1925, 60-mg. doses of ephedrin were given by mouth, but since most of the patients complained of nervous symptoms, 25-mg. doses were used in the season of 1926. Certain patients also were treated by a local application in the form of a nasal spray of a 3 per cent solution of the drug.

Treatment. There were 36 patients in the 1926 series, only 7 of whom were observed in the season of 1925. Therefore, 29 had not used ephedrin previously. Most of the patients were seen when the symptoms of hay fever first appeared, and before they had received other treatment; 11 patients had had preseasonal treatment with only partial relief from symptoms.

Ephedrin was used internally in 25-mg. doses and applied locally in a 3 per cent solution as a nasal spray. Thirteen of the patients used the capsules and the spray, 12 used the spray only, and 11 used the capsules only. Since the effect obtained with ephedrin is only temporary, it is not likely that the effect obtained by its use in one method is influenced by its use several hours later with the other means of administration. Therefore, we have totaled our results from a review of the method of administration rather than from the number of patients treated. This interpretation of results is justified because patients were not treated locally and internally at the same time. We have, therefore, 24 patients who were given the drug by mouth and 25 who were given the nasal spray.

Ephedrin by Mouth. The patients were advised not to take more than two capsules, each containing 25 mg., in twenty-four hours. Only 4 patients used more than two capsules in twenty-four hours; most of them used one or two, depending on the severity of symptoms. Four patients refused to take more than two or three doses because of the resulting severity of nervous symptoms. Most of the patients who took two capsules took one during the morning and one at night before retiring.

The untoward results which followed the oral administration of ephedrin varied greatly with different patients. Nervousness and tremor were the most common symptoms and were noticed in 13

cases. Rapid heart action or palpitation was noted in 5 cases; weakness, faintness, or giddiness in 4; sleeplessness in 2, and increased perspiration in 3. One patient, a surgeon, was considerably inconvenienced by a feeling of incoördination which interfered with work. Two patients felt slightly stimulated following each dose, and 1 complained of nausea.

In 17 cases (70 per cent) the untoward symptoms were either absent or mild, and in 4 the nervous symptoms were more disagreeable than the hay fever. Three patients used the drug only for the more severe paroxysms, as the mild paroxysms caused less discomfort than the drug. Most of the patients noticed that the nervous symptoms were much less marked if the drug was taken just before they went to bed and several patients were able to remain comfortable if they could lie down for from a half to one hour following a dose taken during the day. Careful study of the effect on blood pressure, pulse rate, and so forth, could not be made as our patients were all ambulatory and engaged in their regular duties.

It is obvious that the nervous symptoms produced with the small dosage are entirely out of proportion to those obtained with much larger doses in conditions other than hay fever. In fact, there is little difference in the number of distressing nervous symptoms reported in this series and in that of the previous year when double the dosage was used. We have reported these symptoms as they were given by the patients and, while there seems to be no adequate explanation for the disproportionate effect, our observations suggest the following interpretation: (1) The distressing nervous symptoms bore a distinct relationship to the neurotic tendency of the patient; (2) patients experiencing a paroxysm of hay fever are usually already in a highly nervous state, and (3) the patients treated were all actively engaged.

Results of Ephedrin by Mouth. The results are classified as good, fair and negative. Of the 24 patients, 13 (54 per cent) obtained complete or almost complete relief from symptoms for four hours or more, the average being about six hours. Excessive nasal secretion and irritation stopped, and lacrimation and irritation of the eyes were relieved. Seven patients (29 per cent) obtained only partial relief. In this group are 3 patients who used the drug only for the more severe paroxysms; they felt that the relief obtained outweighed the nervous symptoms produced by the ephedrin. Four patients (16 per cent) were unable to tolerate the symptoms produced by the ephedrin; the results are classified as negative. Even in these cases the symptoms diminished, but the effect was of short duration. Ten patients had asthma with the hay fever. Ephedrin relieved the attacks of 5. Three were moderately relieved, and 2 were not affected.

Ephedrin Administered by Spray. A 3 per cent solution of ephedrin was used as a spray by 25 patients two or three times a day when

necessary. Several of the patients used it oftener, the average being once or twice daily.

Sneezing was practically the only untoward symptom produced, and this was mild in 80 per cent of the cases. Three patients, however, had paroxysms of sneezing lasting from five to thirty minutes. One patient complained of slight stimulation, and another of diuresis.

Results of Ephedrin by Spray. Of the 25 patients who used the drug locally, 7 (28 per cent) obtained marked relief which lasted for several hours; the nasal symptoms were almost completely relieved and the ocular symptoms lessened. It is impossible to ascertain the duration of the drug's effect because of the paroxysmal nature of hay fever. It is probable that the effect of the spray is of short duration and that the comfort for several hours was that experienced by any hay-fever patient between paroxysms, although Fetterolf and Sponsler noted that shrinkage of the mucous membranes persisted for almost three hours. Twelve patients (48 per cent) obtained fair results; some were almost wholly relieved for a short time while others were relieved only partially, but for a longer time. Six patients (24 per cent) obtained negative results, little or no relief, or violent sneezing occurring.

The relief which followed the use of the spray was of shorter duration than that which followed the oral administration, being less than one hour in 44 per cent of the cases. In 11 cases (44 per cent) relief or partial relief lasted from one hour to four hours. In 3 cases the duration of relief was not stated.

The most marked relief occurred in mild cases when the drug was used early in a paroxysm; in the more severe cases, or when the drug was used at the height of a paroxysm much sneezing resulted. None of the patients noticed any increase in symptoms after the beneficial effects of the drug had disappeared. Many patients used the spray for the mild paroxysms and the capsules for the more severe paroxysms. In a few cases of asthma there seemed to be slight relief from bronchial spasm, but this was not definite.

Summary. Ephedrin given by mouth in 25-mg. to 60-mg. doses afforded temporary relief to slightly more than 50 per cent of the patients with autumnal hay fever. An additional 25 per cent obtained sufficient relief to consider its use warranted. Ephedrin given in a 3 per cent solution as a nasal spray is less efficacious and the relief is of shorter duration. However, the majority of patients felt that its use added to their comfort. The best results were obtained when the spray was used early in the paroxysm. The effect of both the local and internal administration seemed to depend on the severity of the paroxysms and the good results were obtained in the milder seizures. Eleven patients who obtained only partial relief from preseasonal treatment were able to control their symptoms with the occasional use of ephedrin. The neurotic temperament and nervous state of the patient are important factors in the

production of tremor, rapid heart action, and other distressing symptoms produced by the drug.

While the value of ephedrin is limited and its effect temporary, our observation of 55 patients during two seasons warrants the conclusion that the drug should be given a definite place in the symptomatic treatment of autumnal hay fever. It is emphasized that when good effects are obtained, they are temporary and symptomatic.

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HAY FEVER AND ASTHMA.

Distribution and Importance of the Acnidas as a Cause of Hay Fever and Asthma in the United States.

By Ray M. Balyeat, M.A., M.D.,

and

T. R. Stemen, B.A., M.A.,

Oklahoma City.

After a study of the hay fever and asthma problem during the past seven years we have learned that western water hemp (Acnida tamariscina) is a very important factor in the cause of both hay fever and asthma in the state of Oklahoma. In other states very little attention has been given to the Acnidas. However, finding western water hemp (Acnida tamariscina) so abundant in Oklahoma, and realizing the part it plays as a cause of both of these syndromes, we cannot help but feel that the importance of this plant and its close relatives, from an allergic standpoint, has been greatly under-

estimated by some of the men working in the field of allergy. A questionnaire relative to the finding and distribution of the Acnidas was sent to the professors of botany of the universities and agricultural colleges of every state. Practically all responded to our first inquiry. Except for the state of Oklahoma and a tier of four or five counties of the neighboring states, which have been carefully investigated by us, the data concerning the distribution of Acnida has been taken from the information received from the professors of botany of the various universities and mechanical colleges.

The map on page 641 shows the distribution of the Acnidas in the United States.

Distribution of Acnida Tamariscina in the United States. The abundance of plant growth of Acnida tamariscina has been investigated very carefully in every county of the state of Oklahoma and a tier of three or four counties in the adjoining states. We have found this plant to be extremely abundant in the central and eastern half of Oklahoma; moderately so along the southern border, and only fairly profuse in the northern and western sections. Over northern Texas and the Panhandle, southern Kansas and western Arkansas, it is quite common. Information received from the botanists in Texas shows that this plant grows throughout the eastern half of the state, but not abundantly. It is sparsely scattered over Louisiana, throughout various sections of the eastern half of Arkansas and Missouri.

Acnida tamariscina was reported by Prof. R. J. Pool, of Lincoln, Neb., as being very prevalent around Omaha, Lincoln and the entire eastern section of the state. It was likewise reported very common throughout the eastern third of South Dakota by Prof. Arthur T. Evans. Mr. R. T. Cratty, curator of botany, of the Iowa State College at Ames, Iowa, reported Acnida tamariscina common throughout the entire state of Iowa, but most plentiful in the southern half. He mentioned the fact in his report that he had always felt that the plant was perfectly harmless. Prof. A. A. Hanson, of Indiana, informed us that it is profuse in certain sections of southern Indiana, but rare in other parts of the state. The plant is found in western Kentucky and western Tennessee along the Mississippi River, but is scarce. It is reported to be found both in Ohio and New York, but the botanists making such reports remarked that it is not a native of their states. Prof. W. B. McDougall stated that the plant had been discovered in many sections of Illinois, but is not very abundant.

Distribution of Acnida Tuberculata in the United States. It is very interesting to find that Acnida tuberculata, a close relative of Acnida tamariscina, has never been found in Oklahoma or any of the bordering states, but it is reported by the botanists of Iowa to be very common throughout the entire state. Dr. C. A. Rosendahl, of the University of Minnesota, wrote us that this plant is

A map showing the distribution of Acnida tamariscina and Acnida tuberculata in the United States. The scarcity and abundance of circles and plus marks are arranged to show the relative profuseness of plant growth in various sections.

plentiful throughout the entire southern and eastern sections of Minnesota, and even as far north as St. Paul. Information from North Dakota shows that it is, likewise, fairly abundant in the eastern third of that state. It has also been found moderately profuse in certain sections of the Michigan Peninsula. Prof. J. J. Davis, of Wisconsin, has found it throughout the southern section of the state, but thinly scattered.

From our survey we have observed that neither Acnida tamariscina nor Acnida tuberculata is a native of any state east or southeast of the Michigan Peninsula except Vermont where it was reported abundant in several sections.

Distribution of Other Acnidas in the United States. The professor of botany of the University of Virginia reported Acnida cannabina in certain sections. Likewise, the botanist from New Jersey informed us that this species of Acnida grows along some of the streams of that state.

Distribution of Western Water Hemp (Acnida Tamariscina) in Oklahoma. The map on page 643 shows the distribution of western water hemp in the various counties of Oklahoma.

In Oklahoma, western water hemp (Acnida tamariscina) is found in every county. In the central and eastern sections it is very abundant. In the northeastern and southeastern parts of the state it is moderately profuse, and also throughout the entire southern portion. In the northern and western sections it is only fairly abundant, except for a few places. In the Panhandle section of Oklahoma it is scarce. The above map shows the relative distribution in every county. On the gumbo land the plant grows in the cultivated fields, after the crops have been laid by, to such an extent that many times it is difficult to harvest the crops. The name western water hemp is a misnomer, as although it grows abundantly in the heavy lowland, it will likewise grow exceedingly well in the sandy soil of the uplands.

The above picture shows the extent of western water hemp growth on upland. It is not found a stalk here and one there, but the plants grow very close together and cover many acres after some of the crops have been removed during midsummer. Botanically speaking, Acnida tamariscina is a branch of the Amaranthaceæ family. In this state, Amaranthus retroflexus and Amaranthus spinosus may be found in every county. In certain sections Amaranthus palmeri is prevalent, but so far as I can estimate, Acnida tamariscina is five hundred times as abundant as all of the amaranths put together. Acnida tuberculata and Acnida cannabina have never been found in this state.

The Botany of the Acnidas. The botany of the Acnida is very similar. Acnida tamariscina is an annual, succulent, and usually very much branched; dicœcious in type and a prolific pollinator. Many of the plants will grow as high as 10 feet. The leaves are

A map of the state of Oklahoma showing the distribution of western water hemp (Acnida tamariscina) in each county.

lanceolate or ovate, 2 to 6 inches long. They are acuminate, but sometimes obtuse at the apex and cuspidate tipped. They are narrowed at the base and the petioles are commonly shorter than the blades. The flowers are small, green, 1 to 3 bracted, in terminal and axillary, continuous or interrupted, spiked and clustered in axils. The staminate flowers consist of five scarious erect one-nerved mucronate sepals which are longer than the bracts. The anthers are two-celled. The pistillate flower is without a calyx, utricle membranous $\frac{1}{24}$ to $\frac{1}{12}$ of an inch long, and circumscissle.

FIG. 1.—A field of western water hemp on the outskirts of Oklahoma City.

Acnida tuberculata is so similar to the Acnida tamariscina that it cannot be differentiated except by examination of the fruit. In the case of Acnida tamariscina the fruit is circumscissle, while the fruit coat of Acnida tuberculata dehisces in an irregular line.

A large number of pollen granules of Acnida tamariscina were measured and they were found to be from 17 to 28 microns in diameter. The average size of the pollen granule is 23 microns. This is about the same size as the pollen from its close relatives, Amaranthus retroflexus and Amaranthus spinosus. The pollen granule is very interesting from a microscopic standpoint, since it is round and has many facets, resembling a golf ball. The amaranth pollen closely simulates that of the Acnidas, but careful examination reveals the difference.

The Importance of the Acnidas as a Cause of Hay Fever and Asthma. One of us recently reviewed 300 consecutive cases of seasonal hay fever that have been tested and treated during the last two years, and the records show that western water hemp was a sole cause in 11 cases, or 3.6 per cent. It was a definite contributing factor in 105 cases, or 35 per cent. About five years ago we became

very much interested in this plant as a cause of hay fever in Oklahoma and the surrounding territory, and have given special study to its distribution and importance in the field of allergy. Since finding it so important as a sole factor or a contributing one in the cause of hay fever cases, we felt that an investigation of the distribution and relative abundance of this plant in various sections of the United States would be worth while.

FIG. 2.—Drawings showing the male plant, staminate and pistillate flower, and pollen of western water hemp (Acnida tamariscina).

Much has been said in the literature and also in pamphlet form from the commercial houses concerning the importance of Amaranthus retroflexus, Amaranthus spinosus and Amaranthus palmeri as a cause of hay fever. Since these plants are all prevalent in Oklahoma, and since we found many patients sensitive to them, we treated a series of 40 cases with an amaranth extract, but obtained poor results in the majority of them. Searching for a cause of our poor results, we noted that the plant life of western water hemp was at least five hundred times as abundant in our state

as all the amaranths put together, and that it was at least one hundred times as good a pollinator as either Amaranthus retroflexus or spinosus. Amaranthus palmeri is a profuse pollinator, equal to that of western water hemp, but it is not very common in most of the counties of Oklahoma. So far as we can determine the amount of pollen from Acnida tamariscina that actually gets into the air is several hundred times greater than the total from all the amaranths. Our estimate of the concentration of Acnida pollen in the air compared with that of the amaranths has to some extent been proved by finding several hundred times more of the former on our plates than the later. The period over which the amaranths and Acnida tamariscina pollinate is practically the same, as is the peak of their pollination, so that an estimate of the relative air content of their pollens by pollen plating is a fair one.

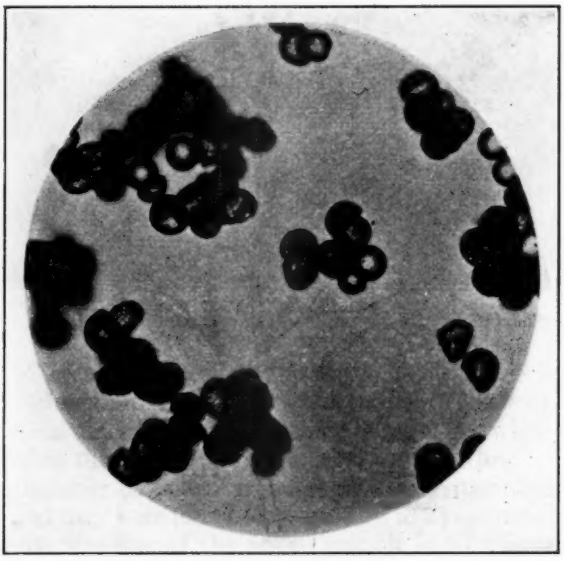

FIG. 3.—Pollen granules of western water hemp (Acnida tamariscina). (X 500.)

We concluded that the cause of our failures in treating the amaranth cases was probably due to the fact that the pollen from western water hemp was the major cause of symptoms in the series studied, instead of amaranth pollen, and that an extract from western water hemp pollen should have been used in the treatment instead of an extract from the amaranth pollen. Later, we recalled about 20 of these cases, retested them, and found the majority sensitive to western water hemp. They were treated with an extract from the pollen of this plant, with pleasing results in most cases.

Since that time, in testing patients we have found nearly all cases who show a reaction to either of the three amaranths also to give a positive reaction to western water hemp. Since we discovered western water hemp to be so much more abundant than the amaranths, and also determined that it pollinates far in excess of them, we use an extract of western water hemp for the treatment of those patients who react to it and also to the amaranths almost as routine.

Knowing what we do about the importance of Acnida tamariscina in Oklahoma and a tier of counties surrounding this state as a cause of hay fever and asthma, we are sure that it is also a very important factor in the eastern half of Nebraska, the eastern third of South Dakota, many sections in Iowa, some in Illinois, and parts of southern Indiana. Since Acnida tuberculata is so closely related to Acnida tamariscina, botanically, it surely must be a factor in the cause of hay fever in the districts in which it is prevalent. Therefore, it is quite probably a factor in many sections of Iowa, southern Wisconsin and eastern North Dakota.

In looking over the literature, we have found little said concerning the Acnidas in relation to hay fever and asthma. Scheppegrell mentions it, and remarks that it is a minor cause of hay fever in moist sections from Illinois to South Dakota. In previous articles one of us has called attention to the distribution and importance of this plant as a cause of hay fever and asthma in our own state and neighboring states.

We trust that the data given in this paper concerning the importance of Acnida tamariscina as a cause of hay fever and asthma in Oklahoma will encourage those working in the states in which it is found to investigate carefully the possibilities of the plant as a source of hay fever and asthma symptoms. May we also suggest to those interested in the study of allergy who live in the states in which Acnida tuberculata is common, that since it is so closely related to Acnida tamariscina, botanically, it is, in all probability, a very definite cause of allergic symptoms and should be thoroughly investigated.

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THE CONDITIONS UNDER WHICH IODIN WILL CAUSE A CHANGE IN THE BASAL METABOLIC RATE IN MAN.

I. Its Occurrence in Conditions Other Than That of Graves' Disease.

By Kirby A. Martin, M.D.,
NEW HAVEN, CONN.

(From the Department of Internal Medicine, Yale University School of Medicine and the Medical Service of the New Haven Hospital, New Haven, Connecticut.)

Introduction. The high incidence of clinical benefit that follows the administration of large doses of iodin to patients with Graves' disease, which is now commonly used as a preoperative measure, seems to be well recognized. Useful as it may be, the procedure is not without danger. However, iodin, when used properly in this connection, is the most valuable therapeutic agent we possess in the treatment of this disease. It will produce a temporary remission of the symptoms in a large percentage of the cases, and bring the patient out of danger almost immediately in the so-called cerebral or gastrointestinal crisis; it lessens the number of operations, shortens the stay in the hospital and lowers the mortality rate.

It is not within the bounds of this communication to discuss the rationale of this method of therapy, nor is it intended to include the complete historical background of iodin in the treatment of this disease. Suffice it to say, iodin has been the active agent in most of the remedies used in the treatment of the diseases of the thyroid for many centuries; it has been used knowingly in the treatment of a clinical condition now known as exophthalmic goiter, or Graves' disease, since Gairdner in 1822 clearly described the symptoms of this syndrome in connection with observations on the untoward effects of iodin in certain cases of goiter, which was thirteen years before Graves described the syndrome. From the earliest record of Graves' disease, now more than a hundred years, a long list of isolated instances can be found in the literature in which distinct benefit has been reported from the use of iodin. The current method of treating this disease is more in accord with that of a hundred years ago than that of two decades ago.

Since Plummer's preliminary report on the beneficial effects of Lugol's solution in the treatment of Graves' disease, a number of papers containing a large number of case studies have been published from several of the large clinics,[2, 3, 4, 5] confirming his observations and adding much information regarding the subsequent course of the disease under this treatment. The conclusions from these publications may be summarized as follows: Iodin, in any form or by any route will produce abrupt remissions in most cases; the remission is in many respects similar to that following a subtotal thyroidectomy, though not so lasting; the maximum effect is usually

reached on the tenth to the fifteenth day; coincident with the clinical improvement there is a lowering of the respiratory exchange; iodin is thought to be the primary cause of the remission; iodin will not suppress the disease permanently; the toxic symptoms will recur even though iodin therapy is continued, but will recur more rapidly when the iodin is withdrawn suddenly; in some cases there is no observable effect from iodin therapy; iodin will usually prevent death from the acute exophthalmic goiter crisis. Associated with the remission of the symptoms there is a simultaneous change in the histologic picture of the thyroid gland from a hyperplastic to a colloidal state.[6, 7]

The clinical course of Graves' disease under larger doses of iodin has been fairly well studied, but the mechanism of the temporary fall in the basal metabolism and subsequent clinical improvement of the patient's condition is not clear. Plummer[1] has supported the view that in Graves' disease the thyroid gland produces an active agent abnormal in quality as well as quantity, which in the tissues of the body causes all the phenomena of the disease. This abnormal product, he believes, is neutralized or inactivated when iodin is given in large doses, resulting in the clinical improvement. This conception is by no means new; it was first introduced by Moebius, in 1886, and is still without scientific proof. The only other explanation that has been offered, so far as is known, is the one suggested by Marine.[8] He believes that the rapid accumulation of colloid in the alveolar spaces of the hyperplastic thyroid following large doses of iodin brings about a pressure retention which temporarily blocks the secretion from the gland.

There is a vast amount of clinical and experimental data in the literature on the thyroid in its relation to iodin, but surprisingly little concerning the explanation of the action of large doses of iodin in Graves' disease. In view of Marine's suggestion it seems worth while to study the effect of large doses of iodin in a few clinical conditions other than Graves' disease upon the basal metabolic rate: (1) Will large doses of iodin in any way alter the basal metabolic rate in any clinical condition other than Graves' disease? (2) Can any additional evidence be brought forward as to the mechanism by which large doses of iodin lower the basal metabolic rate in Graves' disease?

Method. Patients were selected from the New Haven Hospital and Dispensary for respiratory metabolic study as follows: A group in whom there was an increase in the basal metabolic rate which was not primarily due to thyroid disease, that is, leukemia, polycythemia and primary anemia; a group of postinfectious diseases; a group in whom the basal metabolic rate was normal or was at the lower limit of the normal zone, but in whom there was good reason to believe that the iodin content of the thyroid was below the physiologic limit, that is, simple goiter with symptoms of iodin deficiency; a group in whom the basal metabolic rate was below

normal, that is, hypothyroidism and myxedema; a group of normal controls.

The basal metabolism was determined by the Roth-Benedict closed circuit method in the usual way[9] and repeated if good checks were not obtained, or for any reason the determination was questionable. The Tissot[10] apparatus was used on some cases where there was some doubt as to the findings, and also to check the accuracy of the closed circuit method. (It was found that the Roth-Benedict machine checked the Tissot within an average of 3 per cent.) The majority of the subjects were ambulatory, but those that were confined to bed were given at least a week's rest in bed before starting the experiment to avoid confusing changes that might occur from rest alone. As soon as satisfactory and constant readings could be obtained, Lugol's solution was given orally in doses of 5 drops three times a day throughout the experiment. In the beginning the basal metabolism was determined every second or third day; but it was found that, if after the control determination a determination was made about the seventh and fourteenth days the change in the basal metabolic rate, if any occurred, could be detected with practically the same degree of certainty. This procedure was followed for the most part in this study.

Results. There were 29 patients studied, and they included the following: Small cell lymphatic leukemia, 2; polycythemia, 2; primary anemia, 4; acute rheumatic fever, afebrile, 2; normal subjects, 4; simple goiter with symptoms of iodin deficiency, 7; hypothyroidism, including myxedema, all of which had previously had iodin or some thyroid therapy, 3; hypothyroidism, including myxedema, none of which had previously received either thyroid or iodin therapy, 5. The results of the above experiments are found in table (Figs. 1 and 2).

Diagnosis.	No.	Day.	Weight, kilo.	Pulse.	Basal metabolism.
Lymphatic leukemia . . .	15	1	74.0	88	+28.0
	15	7	73.2	90	+30.0
	15	14	71.4	90	+30.0
	22	1	62.0	80	+40.0
	22	7	61.4	84	+37.0
	22	14	60.2	82	+37.0
Polycythemia	10	1	72.0	86	+36.0
	10	7	73.0	88	+34.0
	10	15	72.6	90	+35.0
	17	1	63.0	80	+28.0
	17	7	64.0	84	+32.0
	17	15	62.8	88	+30.0
Primary anemia	9	1	56.7	72	+20.0
	9	7	58.6	64	+23.7
	9	14	59.0	60	+13.0
	27	1	57.8	66	+18.0
	27	7	57.8	64	+ 4.0
	27	14	58.2	62	+ 2.0
	11	1	35.5	82	+12.7
	11	14	35.5	80	+ 1.9
	16	1	60.0	110	+30.6
	16	7	62.4	90	+20.5
	16	14	64.0	80	+ 3.4

Diagnosis.	No.	Day.	Weight, kilo.	Pulse.	Basal metabolism.
Rheumatic fever	8	1	56.4	80	+17.0
	8	7	56.6	70	+ 6.0
	8	14	57.8	64	+ 2.0
	14	1	40.8	100	+18.0
	14	7	40.6	90	+ 6.0
	14	14	42.2	80	0
Normals	12	1	64.5	62	− 3.0
	12	7	64.0	64	− 4.0
	12	14	64.2	64	− 4.0
	13	1	74.0	76	− 2.0
	13	7	74.4	74	− 3.0
	13	15	74.2	70	− 3.0
	21	1	66.0	74	+ 1.0
	21	7	65.5	74	− 1.0
	21	14	65.8	70	− 1.0
	20	1	56.2	76	+ 3.0
	20	7	56.8	74	+ 2.0
	20	14	57.0	74	0
Simple goiter with iodin deficiency	7	1	52.0	80	+ 1.1
	7	7	52.5	66	−17.5
	7	14	53.7	74	− 9.0
	2	1	35.0	100	− 5.0
	2	9	35.5	70	−11.8
	2	16	35.1	64	−15.0
	3	1	52.0	88	+14.0
	3	17	52.0	74	−10.0
	3	20	52.8	60	−14.0
	4	1	35.5	120	− 4.0
	4	8	36.5	80	−17.0
	4	15	37.0	94	− 9.8
	5	1	52.5	80	− 6.0
	5	8	52.0	72	−18.0
	5	15	52.5	76	− 4.2
	6	1	64.0	80	− 4.0
	6	7	64.4	76	−15.0
	6	14	65.0	72	− 9.0
	7	1	38.4	80	+ 3.0
	7	7	38.0	74	−10.0
	7	14	39.5	70	−16.0
Hypothyroidism with previous thyroid therapy	26	1	82.0	58	−25.0
	26	7	81.0	56	−23.0
	26	14	81.8	60	−24.0
	23	1	83.0	60	−18.0
	23	8	82.8	58	−17.0
	23	15	83.4	60	−18.0
	19	1	78.2	54	−17.0
	19	7	77.8	58	−16.6
	19	14	78.4	52	−18.0
Hypothyroidism without previous thyroid or iodin therapy	24	1	60.0	65	−12.0
	24	7	59.6	74	− 4.5
	24	16	58.5	80	+13.0
	18	1	52.2	72	−19.0
	18	7	51.0	80	− 7.0
	18	14	50.0	84	+10.0
	25	1	69.0	60	−22.0
	25	8	68.5	66	− 4.0
	25	14	68.0	80	+10.0
	28	1	49.5	80	−27.0
	28	7	48.6	84	− 7.0
	28	14	47.6	88	+ 7.0
	36	1	58.2	72	−18.5
	36	7	58.0	68	−20.0
	36	14	58.4	70	−19.5

For simplicity of comparison two composite charts have been constructed to show the basal metabolic rate as influenced by iodin therapy during a period of fourteen days in several widely different clinical groups. It will be noted that, collectively, there was a marked variation in their reaction to iodin, but as individual cases in a given group the results were fairly constant.

Lymphatic Leukemia and Polycythemia. (Group 1, Fig 1, Curves 1 and 2.) Patients were selected with lymphatic leukemia[11] and polycythemia[12] who showed a moderately high and constant basal metabolic rate. None of these patients showed any appreciable change, as a result of iodin therapy, in the basal metabolism during the period of observation. It can be demonstrated *in vitro* that fresh blood drawn from a patient with leukemia has a higher

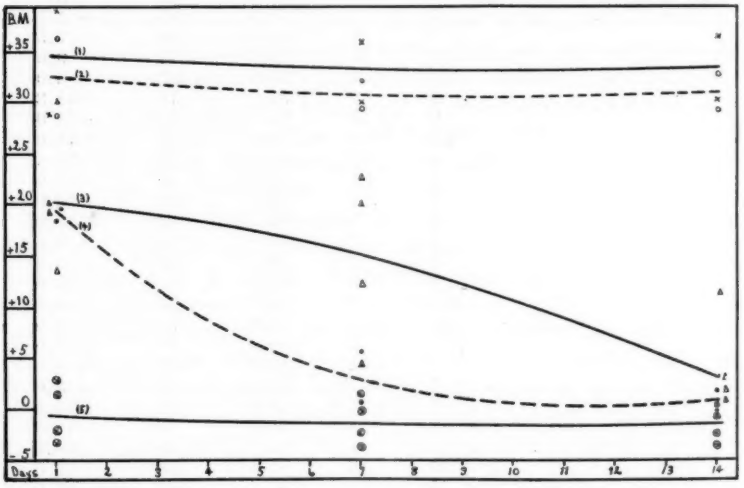

FIG. 1.

rate of oxygen consumption than normal blood per unit length of time. This may partially account for the increase in metabolism in leukemia. However, the primary cause of the increased metabolic rate in neither disease is known.

Primary Anemia. (Group 2, Fig. 1, Curve 3.) It is known that patients with primary anemia frequently have an increased basal metabolic rate, especially during the acute relapses of the disease;[13] but the explanation of the increase is lacking. The patients selected for this group were all in the acute stage of the disease, or relapse. This group showed a moderate but constant fall in the metabolic rate during the period of observation on iodin therapy.

Rheumatic Fever. (Group 3, Fig. 1, Curve 4.) Hospital patients who were convalescing from acute rheumatic fever and

were afebrile were chosen because it was anticipated that they would have a low basal metabolic rate, a finding which has been demonstrated in most postfebrile diseases,[12] and that they would be especially suited for this study because of the duration of the febrile period. A sufficient number have not been studied to warrant any conclusions. It must be borne in mind that this disease manifests itself in cycles, thus, requiring long observation on a large series of cases to be of value. Two of the 3 cases studied, however, had increased basal metabolism instead of a subnormal reading, and the exception later proved to be a case of infectious arthritis with a normal metabolism. So far as is known, the presence of increased metabolism has not been demonstrated previously in acute rheumatic fever, in the afebrile stage and not on any medication. The duration of an increased metabolism in this disease, if this increase is a constant finding, is not known at this time. Both of the cases studied showed a marked and rapid lowering of their basal metabolic rate following the administration of large doses of iodin. The data of these 2 cases are given because of their unusual interest and not with any intention of adding weight to the problem under discussion.

Normal Controls. (Group 4, Fig. 1, Curve 5.) The control subjects studied showed no appreciable change in their basal metabolic rate during the period of observation on iodin therapy. This confirms Reed's[14] recent experiments in which he showed that iodin does not appreciably affect the pulse rate of normal individuals.

Simple Goiter with Symptoms of Iodin Deficiency. (Group 5, Fig. 2, Curve 1.) Patients were chosen for this group who in addition to a simple goiter presented symptoms of iodin deficiency.[15, 16] It must be appreciated that the number of patients suited for this group is necessarily small, even from a large clinic. It will be noted that there was a moderate lowering of the basal metabolic rate during the first week, with a slight rise during the second week.

Hypothyroidism and Myxedema with Previous Therapy. (Group 6, Fig. 2, Curve 3.) This group was composed of patients with a low basal metabolic rate, some of whom showed signs and symptoms of myxedema, and all of whom had either had some thyroid or iodin or both. There was no appreciable change in the basal metabolic rate during the period of observation on iodin therapy.

Hypothyroidism and Myxedema without Previous Therapy. (Group 7, Fig. 2, Curve 2.) This group was composed of patients who had a low basal metabolic rate, some of whom had signs and symptoms of myxedema, but none of whom had previously received any iodin or thyroid therapy. It will be noted that the increase of the basal metabolic rate was very striking during the first week and increased at the same rate to the end of the second week.

Discussion. The change in the basal metabolic rate during the influence of large doses of iodin in the several clinical groups,

as represented by the smooth curves in Figs. 1 and 2 show marked variations as to direction, yet are strikingly similar in respect to the rate of change. In one group the curve shows a marked increase in the basal metabolic rate, others a decrease and still others showed no changes. While there are variations in the direction of the change in the respective curves, the latency with which the change takes place is remarkably constant; in most instances the maximum effect was reached on the tenth to the fourteenth day. The time which is required for these changes to take place, either in a rise or a fall of the basal metabolic rate, suggest a close resemblance to the effect in the basal metabolic rate in a patient with Graves' disease when given large doses of iodin, though not so spectacular. But, in a given case of Graves' disease, it is known that the higher the basal metabolic rate, the greater the improvement, as deter-

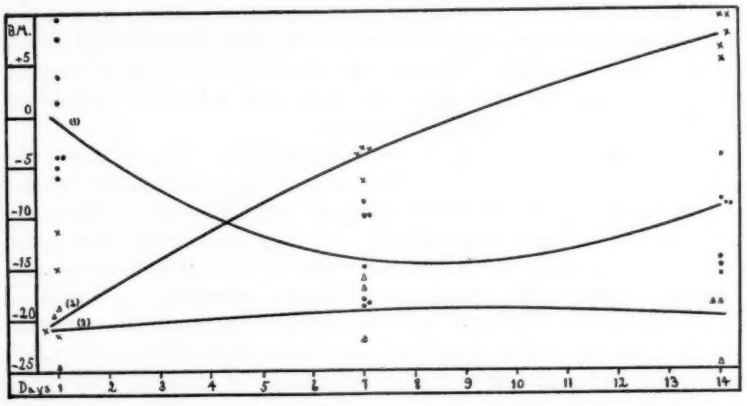

FIG. 2.

mined by the basal metabolism, under any kind of therapy. It is also probably true that a low basal metabolic rate, as in a case with myxedema, as well as a high one, can be made to return to normal more easily than a normal basal metabolic rate can be raised or lowered. This is a factor that has considerable importance in the consideration of the method employed in this study.

The results in this selected group of patients make it perfectly clear that the basal metabolic rate can be made to change by giving iodin in diseases other than Graves' disease. The change is not rapid and transient but slow and very lasting, in contrast to the effect of exercise, food, adrenalin and so forth, and it is not unlike the change in Graves' disease when large doses of iodin are given.

At the present time the means of effecting a great change in the basal metabolic rate, other than a transient change, are as follows: Giving commercial thyroid gland in sufficient doses; giving thyroxin

intravenously in sufficient doses; removing surgically a sufficient portion of the thyroid gland; giving large doses of iodin in any form to patients with Graves' disease whose basal metabolic rate is increased and who have not previously been given iodin for several weeks; ligation of the large arteries to the thyroid gland; rest; and giving ergotamin (24) which is a derivative of ergot. (Sold under the trade name of Gynergen.)

Let us inquire into a few of the factors involved in bringing about these changes in metabolism. In the patient who has a low basal metabolism, whether produced by surgical removal of the thyroid or by a destructive disease of the gland, there is a true hypothyroidism present which is due to the lack of thyroxin, the active hormone of the thyroid gland. If this patient is given commercial thyroid or thyroxin in sufficient doses and a graphic curve of the basal metabolic rate is constructed for a period of twelve to fourteen days, it is found to be similar to the curve of a patient with Graves' disease following a subtotal thyroidectomy,[17] if the former curve is inverted. The inverted curve of the hypothyroid patient on thyroid therapy is also similar to the curve of the basal metabolic rate of a patient with Graves' disease following the ingestion of Lugol's solution.[5] The similarity of these three curves at least suggest a common cause for the change in the basal metabolic rate. In the patient with hypothyroidism the cause is known. The increase of the metabolism was a result of the thyroxin given, contained in the commercial thyroid. In the instance of the patient with Graves' disease, the term hyperthyroidism cannot be justly used because while the disease is, so far as the basal metabolism is concerned, the antithesis of hypothyroidism, yet it has never been demonstrated that there is an increase in the production of thyroxin in this disease. If there is an increase it probably plays but a part in the picture of the disease. However, when a large portion of the gland is removed surgically, or when large doses of iodin are given, the rate of the decrease in the metabolism and the subsequent clinical improvement is such as to suggest a decrease in the amount of thyroxin supplied to the body. In either instance the disease is not cured, but both means serve temporarily to correct the factor which causes the increased metabolism and some of the associated symptoms.

The question then arises as to how iodin alone may change the supply of available thyroxin to the tissues of the body. It was pointed out several years ago that it was possible to relieve the symptoms of hypothyroidism or myxedema by the use of iodin alone when sufficient active tissue is present in the thyroid gland.[18] This statement seems to be well borne out by Group 7 of this series, which was composed of patients with low basal metabolic rate, some of whom had signs and symptoms of myxedema but none of whom had received either iodin or thyroid previous to the experiment. The

subjective as well as the objective clinical improvement was as striking as the improvement in a similar group of patients that had been treated with thyroxin or commercial thyroid gland for at least a few weeks. In contrast to this group, a few patients with the same signs and symptoms including the low basal metabolic rate (Group 6) were treated in the same way, but they showed no appreciable change in the basal metabolism following the administration of iodin. Three of the four patients had been given iodin or thyroid therapy previous to the experiment, the exception being a patient who had a large multiple cystic goiter with a fairly classical picture of myxedema. The failure to obtain any change in the metabolism in this patient was probably due to the fact that there was very little active thyroid tissue present. This does not mean that in a given case with a low metabolism, with or without symptoms of myxedema, the metabolism will be raised when iodin is given, but, if the patient has not previously had iodin or thyroid for a period of weeks, and, if sufficient active thyroid is present, the probabilities are that the metabolism will be increased.

The fact that a hyperplastic thyroid gland can be prevented or made to return to almost its normal state after it has once become hyperplastic, by furnishing it with nothing more than iodin, is of considerable significance. It means that a patient with a simple goiter, if it has not become a resting or colloid goiter, is potentially if not virtually a case of myxedema. The difference is only one of degree.

A decrease in the metabolic rate after the administration of iodin, when the basal metabolic rate is above the normal limits, as in the case with certain patients with primary anemia (Group 2), Graves' disease or when it is lowered from the normal to a subnormal level, as in some cases of simple goiter (Group 4) suggest the possibility of a common explanation.

It is well known that patients with simple goiter have a normal basal metabolic rate but are frequently found to be in the lower zone of normal. The histologic picture of the thyroid gland in the presence of an iodin deficiency is well known and shows no constant difference from the thyroid of Graves' disease.[18, 19] It is also known that patients dying from primary anemia as well as from long period of febrile illness frequently show varying degrees of thyroid hyperplasia, probably as the result of an absolute iodin deficiency from the prolonged increased metabolism.

The symptoms and subsequent course of these patients whose metabolic rate has been decreased by iodin are quite similar to those of a typical case of Graves' disease with a subtotal thyroidectomy, so far as the basal metabolism is concerned; and for all practical purposes this is probably just what happened. The exact way in which the thyroxin is released from the thyroid we do not know, but it is agreed by most investigators that the thyroxin is stored in

the colloidal portion of the gland. Since there is evidence of an acute retention of colloidal material in the alveoli when large doses of iodin are given, it seems reasonable to assume that there is likewise a retention of thyroxin. The distended alveoli of the gland will finally reach an equilibrium and the thyroxin will again be gradually released. This assumption is borne out by the fact that iodin does not suppress the symptoms permanently in Graves' disease. The curves of the metabolic rate in the cases studied agrees with retention and a release of the thyroxin as described. It seems justifiable to state that the cases studied, which are not primarily thyroid disease, show changes in their basal metabolic rate as result of a similar mechanism. If the thyroid gland could have been examined in these patients before and after iodin therapy, they would probably have been found to differ from the thyroid hyperplasia of Graves' disease only in degree.

Marine[20] has repeatedly described the histologic picture of the hyperplastic thyroid gland of various experimental animals before and after iodin administration. Cattell[6] and Reinhoff[7] have made a careful study of the thyroid gland removed surgically from patients with Graves' disease who had been prepared for operation by receiving large doses of iodin. The work of the latter author is of particular interest because he removed control specimens of the thyroid before iodin was started. Reinhoff demonstrated, as Marine had done in animals, that the hyperplastic thyroid is converted into a colloidal goiter. It is generally accepted that a hyperplastic thyroid gland is an iodin-poor gland; and, if iodin is given in the presence of this type of gland, there will be a rapid accumulation of colloid in the alveoli, induced by the iodin, increasing their size and converting the high columnar epithelial lining of the alveoli to a low cuboidal lining. This picture has been described as one of acute retention of colloidal material.[8] It has not been uncommon in clinical experience to see patients with an acute enlargement of the thyroid and having considerable discomfort from it following the ingestion of large doses of iodin. This is the picture of the so-called "iodin thyroiditis" described in the older literature.

The assumption that Graves' disease is caused by abnormal thyroxin has little or no support. It has been demonstrated that if the thyroxin molecule is changed in the least, that is, by substituting an acetyl radical for one of the hydrogens of the amino group, producing acetylthyroxin, the substance is without effect upon the heat production in man.[21, 22] Marine[8] has fed thyroid of Graves' disease to patients with Graves' disease demonstrating that it has not only no toxic substance in it, but that it has very little iodin, and that it is practicllly without effect upon the basal metabolism. Sturgis[23] has shown that iodin has no effect on the toxic symptoms induced in rabbits by intravenous thyroxin. If there is an abnormal toxic

substance present, and iodin neutralizes this substance, the disease should be permanently cured as along as there is a sufficient supply of iodin present, but unfortunately the disease is not cured by this procedure.

By giving iodin, a hyperplastic thyroid gland of Graves' disease can be converted into a colloid goiter with or without change in the basal metabolic rate or the symptoms of the disease. This may be accomplished by giving iodin to a patient with this disease either in small amounts or in large amounts. If a small amount of iodin is given over a long period of time the transition of the hyperplastic gland to a colloidal state is so gradual that the function of the thyroid is not disturbed. This seems to be strong evidence against the presence of an incompletely ionized thyroxin or the histologic picture of the thyroid having anything to do with the cause of this disease. If large doses of iodin are given for a few days, the thyroid accumulates such a large amount of colloidal material in the alveoli in such a short time that it is functionally incapacitated for a time. This would seem to be strong evidence in favor of the fall of the basal metabolic rate and improvement of the symptoms being due to a sudden withdrawal of thyroxin to the body.

The clinical differentiation of adenoma from other enlargements of the thyroid, by their reaction to iodin, is not so clear cut as one might be led to believe from the recent literature on this subject. Pathologists inform us that there is a fairly gradual transition from the diffuse, uniform hyperplasia of simple goiter to the definitely encapsulated masses of typical adenoma. In the light of the present experiments the fallacy of attempting to differentiate between the so-called toxic adenomas and Graves' disease as well as other diseases of the thyroid, by using iodin as a diagnostic test can at once be appreciated. The extent to which iodin will effect the basal metabolism in a given case seems to depend upon the ability of the patient's thyroid to store iodin. These experiments also serve to clarify our conception of the heretofore seemingly paradoxical action of iodin in different diseases of the thyroid gland, and, to show that iodin is not specific for Graves' disease in lowering the basal metablism but that it will likewise lower the basal metabolism of a patient supposedly who has a hyperplastic thyroid gland, regardless of the disease, that is capable of storing iodin.

Summary. 1. The effects of large doses of iodin on the basal metabolic rate in patients with leukemia, polycythemia, primary anemia, rheumatic fever, simple goiter and hypothyroidism have been studied.

2. Iodin will lower the basal metabolic rate in clinical conditions other than Graves' disease.

(*a*) The increased metabolic rate of patients with leukemia and polycythemia was not affected by iodin.

(*b*) The high basal metabolic rate of patients with primary anemia

and rheumatic fever was lowered, similar to the results seen in Graves' disease when iodin was given.

(*c*) Moderate but constant lowering of the basal metabolic rate, from the normal to a subnormal level, was observed when iodin was given to patients with simple goiter showing symptoms of iodin deficiency.

(*d*) Iodin alone will frequently greatly increase the basal metabolic rate in patients with hypothyroidism or myxedema providing they have not previously had iodin or thyroid therapy for several weeks.

3. The mechanism by which the basal metabolic rate is lowered, following the ingestion of large doses of iodin, would seem to be from an acute mechanical blocking of the thyroid secretion.

4. The extent to which iodin will affect the basal metabolic rate in any patient probably depends upon the ability of the patient's thyroid to store iodin.

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EPIDEMIC ENCEPHALITIS.

An Analysis of Fifty Cases.

By Thomas P. Sprunt, M.D.,
BALTIMORE.

(Read before the American Climatological and Clinical Association, Philadelphia, September, 1926.)

Almost a decade has passed since cases of epidemic encephalitis became relatively numerous, and a number of interesting problems remain to be settled in the etiology, the epidemiology, the diagnosis, the prognosis, and in the treatment of this lamentable malady. It may be helpful to review our experience with certain phases of the disease. My remarks shall be based entirely upon the study of a series of 50 cases.[1] Only those cases were selected in which there could be no reasonable doubt as to the correctness of the diagnosis. No merely suspected cases or cases in which encephalitis was a probability were included. Practically all the patients represented in this series were in the chronic stages of the disease, since in these cases a more nearly complete clinical study was made and the clinical data seemed, therefore, to be the more promising.

The study of these cases throws no light whatever upon the direct or exciting cause of the disease, but we have been for some years particularly interested in the predisposing causes of disease or in the constitutional study of patients, especially those suffering from chronic ailments. It seems to us altogether unlikely that we are all equally susceptible to epidemic encephalitis and the incidence of the disease would, of course, indicate that the great majority of the population are immune. Our analysis, however, throws practically no light upon this important factor.

[1] From the private clinic of Drs. Barker, Cross and Sprunt and associates, Baltimore.

Investigation into the family histories of the patients with special regard to a tendency to the development of nervous symptoms revealed the fact that in only 7 cases was it evident that the family stock was tainted in this respect.

There were thirty-one men and nineteen women in this series, a difference that in this small number of cases may not be of significance.

The age of the patients ranged between twelve and sixty-nine years, the great majority falling within the third, fourth and fifth decades.

Judged at least by rather crude standards, the habitus of the patient seems to be of no consequence. From the standpoint of nutrition at the time of the first examination, 19 of the patients came within the normal weight zone, 12 were overweight and 19 were underweight.

Investigations into the personal history of each patient for evidence of a nervous trend, including migraine and other such disturbances, show that 21 of the patients, less than half of the series, gave a history of autonomic or other nervous imbalance. This is not, we think, a particularly significant figure.

The ordinary poisons seem to play no rôle as predisposing causes of encephalitis. Only 8 of the patients admitted the use of alcohol and in 6 of these very little alcohol was taken. Twenty of the patients used tobacco in some form, and 6 of these used it in extreme moderation.

Of previous diseases none seemed important with the possible exception of influenza and of focal infections. Thirty-two of the patients said that they had had influenza, but closer questioning frequently raised the suspicion that the symptoms considered by the patients evidences of influenza may really have been the acute symptoms of onset of the encephalitis. As in all such series of cases focal infections were common enough. In only 6 was there no evidence of past or present infections of this sort.

In regard to the time of occurrence of the original symptoms, 2 of the cases had their onset in 1917, 5 in 1918, 9 in 1919, and 19 in 1920, the remainder beginning since that date.

The diagnosis at the onset of the disease may be very difficult, and it seems quite certain that many of the milder cases are entirely unrecognized at that stage; indeed its recognition may be quite impossible in the absence of sufficient neurologic signs or symptoms to indicate that the nervous system is disturbed by more than the ordinary toxemia of an acute infection. In the anamneses of these patients some of the more important features were fever in 35 cases, diplopia in 30, some type of sleepiness in 27, insomnia in 24, delirium in 14 and ptosis in 10. One or two striking features might remain in the patient's memory, as, for example, a sudden attack of extreme vertigo with resultant nausea and vomiting or a period of several

days during which there were lancinating pains in the extremities and some blurring of the vision.

There may be no prodromal symptoms. Some of the fulminant cases seem to begin like a flash of lightning from a clear sky. A patient, having felt quite well the day before, may awake at night because of some discomfort and by morning the symptoms and signs are sufficiently marked to make the diagnosis easy. In another type, there may be a definite prodromal period of several days with malaise, mild gastrointestinal symptoms, perhaps very slight visual disturbances and then some striking symptom that makes the victim realize that he is ill. In still another type, the onset is so insidious that in retrospect the patient has no idea when the disease began. Even in definitely progressive cases, there is often the history of remissions with periods of few or no symptoms interspersed with periods of illness that may show decided differences from each other in respect to neurologic localization.

Among the clinical neurologic features during the chronic stage at which they were first examined in the clinic there is the usual striking predominance of motor signs and symptoms, 48 of the patients showing some form of motor disturbance. Of these, 30 presented the Parkinsonian syndrome, 10 had myoclonic disturbances, and in 5 there were paralyses. Only 15 of the patients gave evidence of sensory disturbances; of these 9 had pain, 6 paresthesias, and 3 asynergy.

There are thirty-two records of cerebrospinal-fluid examinations, with the variation in the findings that one might expect owing to the different stages of the disease and different localizations within the nervous system. The pressure is recorded as normal in 18, increased in 6 and diminished in 5. There was pleocytosis, that is 10 cells or more per cubic millimeter, in only 4 of the cases. The amount of globulin was greatly increased in 4, was somewhat increased in 9, a trace appeared in 8 others, and was said to be negative in 11 of the cases. An estimation of the amount of sugar present in the cerebrospinal fluid was made in 11 of the cases; in 10 of these the sugar values were 70 mg. per hundred cubic centimeters or more.

Signs of a disturbance in the autonomic nervous system were less frequent than had been expected. The autonomic nervous system was investigated by study of the pupils, the moisture or dryness of the skin, the secretions of the salivary glands, the pulse rate, the blood pressure, disturbances of respiration, the degree of gastric acidity, and the motility or tonicity of the musculature of the stomach and of the colon by roentgenoscopic and roentgenographic examinations.

In the examination of the pupils, mydriasis was encountered 19 times and myosis only once. There was anisocoria in 8 cases. In 10, the pupils were sluggish in their reaction to light and in 1 the pupils were fixed.

There was evidence of hyperhidrosis in 5 cases and of dry skin in 4 of the patients. Otherwise the skin was not remarkable.

Sialorrhea was present ten times and dryness of the mouth once.

Respiratory disturbances were present in 5 cases.

Study of the circulation and of the gastrointestinal tract shows no significant variations from what might be expected in any series of 50 cases.

The basal metabolic rate was determined in 18 cases; it was accelerated in 2, retarded in 3 and normal in 13. The basal rate is of particular interest in the Parkinsonian patients in view of the usually marked increase in the tonicity of the skeletal muscles and of the frequent presence of tremor. The rate was determined in 11 of the Parkinsonian cases; it was accelerated in 2 and within the normal limits in 9. In 1 case with a basal rate of + 17 there was no satisfactory explanation of this rate with the possible exception that the test was performed during very hot weather. The second case showed a rate of + 25 per cent and + 30 per cent respectively in the two tests; this occurred in the case of a woman aged forty-seven years, who was 10 pounds over her calculated ideal weight, showed a slight tachycardia and an arterial hypertension with blood pressure 200 systolic and 130 diastolic. There were no other definite signs of toxicity of the thyroid.

The view has been advanced that patients with the Parkinsonian syndrome show more evidences of disturbance in the autonomic nervous system, or that patients with labile autonomic nervous systems are more prone to develop the Parkinsonian picture. Separate analysis of the Parkinsonian cases of this series indicates that there are no important variations in the behavior of the autonomic nervous system with the exception that all of the cases showing sialorrhea were of this type.

The blood as a rule was normal. Ten cases showed a moderate anemia, with hemoglobin of less than 80 per cent.

This series is not adapted to the study of the general prognosis of encephalitis during the acute phase of the disease. There is one feature of interest, however, in this connection. If we accept the Parkinsonian picture as the most malign of all the subsequent chronic manifestations and if we divide the cases according to the history of severity of onset, we find that of those with severe grades of onset 77 per cent later developed the Parkinsonian syndrome; of those with onsets of medium severity 57 per cent developed this picture; and of those with mild onset only 28 per cent. It would seem, therefore, that at the acute stage of the disease the probability of the development of a Parkinsonian syndrome varies directly with the severity of the symptoms of onset.

These 50 cases were all seen in the chronic stage of the disease, at varying periods after the onset. We have satisfactory information of the present condition of 35 of these patients four to six years

after their first examination in this clinic. Twenty-five of these were of the Parkinsonian type. Only one patient has died, and that one by suicide. Twenty-two of the patients may be considered improved and 13 as unchanged or worse. Eight of the patients are practically well, although several of them are scarred in some particular. One of the Parkinsonian patients recovered; this man developed the Parkinsonian picture within a few months of the initial symptoms and had apparently recovered entirely within fifteen months. Three of the 8 patients had mild symptoms of onset, 3 had onsets of medium severity, and in 2 the symptoms of onset were severe. In addition to the 8 cases mentioned above, 4 patients are able to work although they are not well. Ten patients have shown some improvement but are still chronic invalids. In summary, one may say that of the 35 patients successfully followed 1 has died by suicide, 12 are able to work, and 22 are chronic invalids more or less completely incapacitated.

The treatment instituted for those patients who remained under our care, or advised for those who did not continue under our observation, included as a most important factor, rest both physical and mental. In some cases there was a preliminary period of complete rest in bed; with most of the patients, however, a half rest regimen was instituted, with their activities gradually increased as their symptoms permitted. Care was taken that their responsibilities should be as light as possible and increased only with their ability to handle them satisfactorily. We have found that judicious psychotherapy is of great assistance in helping to relieve the patients of the frequent superimposed psychoneurotic symptoms and in aiding them to adapt themselves to their handicap more successfully.

Easily accessible focal infections were removed or treated.

The diet was arranged to promote the proper degree of nutrition, to furnish a satisfactorily balanced ration and to care for the excretory functions.

Muscle training, massage and baths were useful in many cases.

In the symptomatic pharmacotherapy, various sedatives and analgesics were used. In the Parkinsonian cases, no drug was found to compare with hyoscin hydrobromid in efficiency in relieving the hypertonicity of the muscles, reducing the tremor and stopping the sialorrhea. It has been our impression that the doses generally used are too small. When sufficient amounts are given many of these patients experience decided relief and are much more comfortable, even though they must still remain in the chronic invalid division. It was our custom to begin with $\frac{1}{200}$ of a grain by mouth three times a day, increasing to $\frac{1}{150}$ of a grain three times a day and then to $\frac{1}{100}$ of a grain three times a day. A number of the patients received $\frac{1}{75}$ of a grain three times and several of them $\frac{1}{75}$ of a grain four times a day. We have not used larger doses but have seen

some of Hohman's patients that have taken $\frac{1}{50}$ of a grain, and even $\frac{1}{30}$ of a grain four times a day, with apparent benefit.

Summary. An analysis was made of 50 cases with the chronic manifestations of epidemic encephalitis.

There was brought out no definite evidence of a constitutional predisposition to nervous or infectious disease.

The diagnosis in the early stage of the disease may be very difficult or really impossible. In the anamneses of patients with more striking symptoms of onset those symptoms were in the order of frequency: fever, diplopia, somnolence, insomnia, delirium and ptosis.

There is a great predominance of motor over sensory disturbances. Cerebrospinal-fluid examinations are useful in diagnosis chiefly in ruling out other possible diseases of the nervous system.

There were few marked disturbances of the autonomic nervous system. Mydriasis was noted in 19 cases and sialorrhea in 10. The basal metabolic rate is not significantly changed.

From the standpoint of prognosis it would seem that at the acute stage of the disease the probability of the development of a Parkinsonian syndrome varies with the severity of the symptoms of onset.

Of 35 patients successfully followed, 1 died by suicide, 12 are able to work and 22 are chronic invalids.

Important points in treatment are rest, freedom from too much responsibility, psychotherapy, the dietetic and hygienic regimen, mechanotherapy and hydrotherapy, and sedative pharmacotherapy, especially the use of hyoscin hydrobromid in the Parkinsonian cases.

THE GENUS PROTEUS IN MENINGITIS.

By Josephine B. Neal, M.D.,

and

Harold Abramson, M.D.,

new york city.

(From the Meningitis Division, Department of Health, City of New York, and Beth Israel Hospital.)

An extensive investigation of the proteus group was made by Wenner and Rettger[1] in 1919. This has done much to clarify the classification of this very heterogeneous group of organisms. From their work on eighty-four strains collected from various sources they drew the following conclusion:

"The types Proteus vulgaris Hauser, Proteus mirabilis Hauser, and Bacillus proteus are, with a few exceptions, identical. The genus proteus should be limited to organisms of this group. Proteus zenkeri is identical with Bacillus zopfii and therefore should

not be grouped with the proteus genus but rather with Bacillus zopfii, the organisms of this type forming a genus to be known as zopfius.

"The organism Proteus fluorescens Jaeger does not resemble the proteus genus, but rather the fluorescent group (genus pseudomonas) and should not be known by the name proteus.

"The proteus genus comprises a large group of organisms which can be subdivided on the basis of their action on maltose into two distinct species. For the species fermenting this sugar the name Proteus vulgaris is suggested, and for the species failing to attack it the name Proteus mirabilis."

The organisms of the genus proteus are small, actively motile Gram-negative rods, occurring singly, in pairs or in chains. They liquefy gelatin and grow readily and rapidly in ordinary culture medium at room temperature.

These organisms are widely distributed in Nature, being almost constantly present in putrefactive organic matter of animal origin, in soil contaminated by animal excreta, in stagnant pools and in sewage.

The genus is usually regarded as nonpathogenic, but its occurrence either in pure culture or associated with other organisms is not infrequently reported in various pathologic conditions. Park and Williams[2] state that it appears to be next to the Bacillus communis in the etiology of cystitis and pyelonephritis and that it is sometimes the predominating organism in cholera infantum.

The genus proteus has been found in war wounds in as high a case rate as 24 per cent. It is also reported from cases of otitis media and brain abscess.

As a causative factor in meningitis the genus proteus seems to be rare. In a series of nearly 2000 cases of various kinds of meningitis seen by members of the Meningitis Division, Research Laboratory, Department of Health, New York City, it has been found only twice. In both these instances it was associated with another organism.

Cases in the Literature. A search of the literature reveals only 7 case reports of meningitis due to the Genus proteus.

CASE I.—Reported by A. E. Ross[3] in 1912. A male child, aged nine months, who died after an illness of about six days. There had been typical signs and symptoms of meningitis. From the spinal fluid an organism was isolated, the cultural characteristics of which were those of Proteus mirabilis. The patient's serum showed definite agglutination with the organism isolated from the spinal fluid. The necropsy revealed a thick layer of greenish-yellow pus covering the entire surface of the brain and spinal cord. The ventricles were dilated with a purulent fluid. Both middle ears contained pus and there were evidences of enteritis in both the large and small intestines.

CASE II.—Reported by F. Goebel[4] in 1914. This was a male infant that died at the age of nine days, meningeal symptoms being present practically from birth.

A Gram-negative bacillus liquefying gelatin and growing readily on ordinary media was isolated from the spinal fluid. This organism was identified as belonging to the genus proteus.

A generalized meningitis was found at necropsy. No other pathologic lesions were demonstrated.

CASE III.—Reported by A. Bauer[5] in 1918. This was a fatal case of meningitis secondary to otitis media. A Gram-negative bacillus of the genus proteus was isolated from the spinal fluid. It was evidently Proteus mirabilis as it did not ferment maltose.

CASES IV AND V.—Reported by J. M. Anderson[6] in 1921. These were young adults in Constantinople. Both these cases were diagnosed as typhus fever on account of the positive Wilson-Weil-Felix reaction. In the first case there were typical signs of meningitis and from the spinal fluid Gram-negative motile bacilli were cultured which were apparently identical and which belonged to the genus proteus. One patient recovered and the other died after an illness of nine days. It is interesting to note that in each case the patient's serum agglutinated organisms isolated from his spinal fluid in the same titer as it agglutinated the Bacillus proteus X19 used in the Weil-Felix reaction.

CASE VI.—Reported by J. D. Kernan[7] in 1922. This was a fatal case in a young adult probably secondary to a peritonsillar abscess. There was an infected thrombus of the left jugular vein extending into the sinuses. There was also an abscess of the left temporal lobe of the brain. In addition to these lesions, there was pleurisy, pneumonia and a lung abscess. A proteus was isolated in pure culture.

CASE VII.—Reported by Bischoff and Brekenfeld[8] in 1925. They reviewed the literature of Proteus meningitis in infants, reporting Cases I, II and III and adding 1 case of their own. This was a girl, aged three and a half months, who died after an illness of seven days. Typical signs of meningitis were present. From the spinal and the ventricular fluids a proteus was isolated. This organism showed a high agglutinating titer with the patient's blood. A similar organism was found in preparations from the large and small intestines.

In these 7 cases the genus proteus alone was found in the spinal fluids.

The Meningitis Division has studied 2 cases of meningitis in which organisms of the genus proteus occurred, but in each case another organism was present also.

Case Reports. CASE I.—M. S. a male infant aged five and a half weeks was first seen, November 15, 1926. The delivery was normal and the child appeared to be well until November 6, when he became

suddenly ill, with vomiting restlessness and fever. He was constipated and the stools were greenish. In a few days frequent and severe convulsions developed. On examination it was found that the fontanelle was bulging, there was a slight Brudzinski sign, the pupils were contracted and equal, the ears were normal, the patellar reflexes were present and equal, the heart, lungs and abdomen were normal. The temperature had ranged from 101° to 103° F. On lumbar puncture only a few drops of very purulent, bloody fluid could be obtained. A smear of this fluid showed numerous Gram-negative bacilli both intracellular and extracellular, and on culture both a Gram-negative bacillus and a Gram-positive coccobacillus. As this proved that a meningitis was present and adequate relief of pressure could not be obtained by lumbar puncture, either because the fluid was too thick or because there was blocking, the right ventricle was punctured on November 16, 15 cc. of yellowish, cloudy fluid being obtained. This fluid showed a very great increase in cells, practically all polymorphonuclears, Gram-negative bacilli both intracellular and extracellular and a few Gram-positive coccobacilli, mostly intracellular by a smear and similar organisms by culture. The albumin and globulin were greatly increased and the sugar was diminished. On November 17 the left ventricle was punctured, yielding 35 cc. of yellowish, purulent fluid. This fluid was similar to that withdrawn on the previous day except that the sugar was still more decreased. The ventricle was irrigated with a modified Ringer's solution. A similar procedure was carried out on November 18 and 19. During this time the condition of the child remained practically unchanged. The convulsions were still frequent and severe. The constipation noted early had disappeared and there were frequent greenish stools of foul odor.

On November 20, the patient was admitted to Beth Israel Hospital on the service of Dr. Alfred F. Hess. The examination showed only slight changes from those already described. The head was now retracted, and the neck rigid. The pupils were dilated and equal. The liver was enlarged.

At the hospital daily ventricular punctures were performed on alternate ventricles and irrigation with Ringer's solution was done. At first the fluid, greenish-yellow in color and turbid, came out under high pressure. Later, however, the pressure became markedly decreased and it was necessary to pass the puncture needle deeper into the ventricles in order to obtain the fluid, which soon became bloody and contained many flocculi of thick pus. A fluid obtained on December 21 showed that the Gram-positive organism had disappeared from the fluid but the Gram-negative bacilli were still there in large numbers. Attempts to obtain fluid by lumbar puncture were unsuccessful.

The general condition of the child remained remarkably good. The weight at birth was 8 pounds 2 ounces, and at the time of its

death, January 8, 1927, it was 7 pounds 7 ounces. The convulsions were readily controlled by chloral by rectum, though they increased in frequency and duration toward the end. The temperature was low and irregular. Much of the time it was less than 100° F. But it occasionally ranged between 100° and 103° F.

The following blood counts show the changing blood picture and especially the progressive anemia.

	Nov. 22, 1926.	Nov. 26, 1926.	Dec. 6, 1926.	Dec. 12, 1926.	Jan. 4, 1927.
Red blood cells	4,250,000	4,660,000	...	...	2,650,000
Hemoglobin	75 per cent	80 per cent	...	...	50 per cent
White blood cells	19,300	38,900	9400	11,000	10,400
Neutrophils	68 per cent	82 per cent	62 per cent	47 per cent	81 per cent
Transitionals	...	...	3 per cent	7 per cent	
Large lymphocytes	...	...	...	5 per cent	
Small lymphocytes	26 per cent	18 per cent	35 per cent	41 per cent	19 per cent
Mononuclears	6 per cent				

The Wassermann was negative.

The Gram-negative bacillus was actively motile and grew readily at room temperature on agar plates, rapidly spreading over the surface. It liquefied gelatin. On Russell, the slant showed no change but there was acid and gas in the butt. Due to a misunderstanding the culture was not tested on maltose so it must be classed only as belonging to the genus proteus.

The Gram-positive bacillus was short, appearing somewhat coccoid in form while in the mixed culture. When isolated, it was found to be nonmotile. It did not liquefy gelatin. It grew readily at room temperature in ordinary media. It produced acid in glucose, lactose, and saccharose. It could not be exactly classified but it resembled very closely Bacillus segmentosus.

This case was remarkable for its long course (nine weeks). In all the other cases reported, the duration of the illness was much shorter.

Case II.—The other case seen by the Meningitis Division in which the genus proteus occurred was that of W. B., a negro aged forty-six years. He was admitted to Bellevue Hospital June 4, 1926, with a history of a chill and fever, pains in chest and legs, bloody sputum, headache and stupor lasting for three or four days. On admission, there were definite signs of pneumonia in the left lower lobe and also a positive Kernig sign and stiffness of the neck. Lumbar punctures, yielding cloudy fluid, were done on June 6, 7, 8 and 9. When examined on June 8, he was stuporous and unable to coöperate. There were definite signs of meningitis. The temperature had been ranging between 100° and 105° F, the pulse between 80 and 130, the respirations between 20 and 32. He died

on June 9. On June 8, 3 cc. of very purulent spinal fluid could be obtained. This showed in the smear Gram-positive cocci and Gram-negative bacilli. On culture, the Gram-positive cocci were found to be Staphylococcus aureus and the Gram-negative bacillus, Proteus mirabilis. It was actively motile, grew readily on ordinary media at room temperature, liquefied gelatin and did not ferment maltose.

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ETIOLOGY OF GRANULOMA INGUINALE.

With Report of Eighteen Cases.

By Meredith F. Campbell, M.D.,
NEW YORK.

(From the Urologic Service of Bellevue Hospital.)

Recently McIntosh[1] reported experimental studies on the nature and transmissibility of the causative agent of granuloma inguinale. He deduced from these observations that the so-called Donovan bodies, usually found as intracellular inclusions in this disease, were thereby conclusively established as the etiology. Others,[2] by rabbit injection, believe they have produced lesions comparable to human inguinal granuloma. Some time ago, when engaged in the study and treatment of a number of patients admitted to the Urologic Service of Bellevue Hospital with this disease, we became interested in the etiologic aspect of the problem. To this end we carried on a rather extensive experimental study, not only in animals but in humans, directing our attention particularly to the transmission of the disease. The results of these experimental observations are here recorded together with a brief résumé of 18 cases treated in Bellevue Hospital since 1919 when 2 cases were reported from this institution by Symmers and Frost.[3]

Granuloma inguinale is definitely established as a clinical entity and is acquiring a literature of its own with surprising rapidity. Most of the reported cases have been negroes; the white race is rarely attacked. Geographic incidence is greatest in the subtropics

but we have seen some patients who have never been outside New York City.

The disease begins as a small moist papule which rapidly ulcerates with progressive and eccentric invasion of the surrounding tissues by an elevated, reddish, often shiny, delicately skinned granulomatous proliferation, superficially ulcerating when moist, cracked when dry. Usually, however, the lesions are moist and a thick mucoid exudation possessing a peculiar stench, somewhat like dead fish, is characteristic. The disease shows no tendency to spontaneous healing. The genitals and perigenital tissues are most often involved although lesions have been seen on the face and neck. Males are more frequently attacked than females.

The disease spreads by auto-inoculation and peripheral extension and is usually of greatest severity along skin folds, particularly the inguinal and gluteal. It is extremely interesting, however, to note the patchy distribution often observed over the dependent genitalia. Inoculation by clothing transmission and friction is the probable explanation. The disease is in no sense venereal. Examinations of the wives of two of our patients presenting the filthiest of lesions and exercising frequent cohabitation failed to show lesions of granuloma inguinale. Infection by sexual contact has never been proven. Adenopathy is characteristically absent although the occurrence of elephantiasis of the genitalia, or at times of a leg, signify lymph channel involvement. These patients are singularly free from discomfort. An itching or at times a burning sensation plus the presence of the lesion and its accompanying foul discharge constitute the chief complaints. The lesions themselves are but mildly sensitive.

Conditions from which granuloma inguinale must be differentiated are: (1) Chancre—this is a sharply defined punched out ulcer with a characteristically firm induration and associated lymphadenopathy; (2) chancroid—acutely tender ulceration with marked glandular involvement; (3) gumma—a deeper involvement, does not bleed freely and usually accompanied by a positive Wassermann; (4) tuberculosis—in the absence of demonstrable tubercle bacilli or positive animal inoculation, a biopsy specimen is the most reliable means of diagnosis; (5) malignant growths (epithelioma or carcinoma) are characteristically more indurated, and the histologic picture of neoplasm is diagnostic.

Since the first description of the condition by Conyers and Daniels[4] (1895) the etiology has been uncertain. They believed it to be tuberculous. Some[5, 6] conceived it luetic, having demonstrated Spirochæta pallida. MacLennon[6] found Spirochæta refringens. In 1905 Donovan[7] described peculiar ovoid inclusions within the large mononuclear cells present in the lesions, to which organisms his name is given. Morphologically, these inclusions are encapsulated Gram-negative coccoid or coccobacillary forms whose place

CASES OF GRANULOMA INGUINALE FROM BELLEVUE HOSPITAL.

No.	Name.	Sex.	Occupation.	Marital.	Race	Age.	Nativity.	Admission date.	Duration.	Location.	Wassermann.	Antiluetic treatment.	Other treatments.	Donovan bodies found.	Tartar emetic, 1 per cent.		Comment and results.
															Amount, cc.	Treatment, times.	
1	W. W.*	♂	Chauffeur	S	C	29	So. Carolina	Dec. 15, 1919	1½ yrs.	Penis, scrotum, thighs	−	0	0	‡	0	0	This was the first case to be recognized as granuloma inguinale at Bellevue; no treatment other than local given, patient dying of sepsis.
2	F. B.*	♂	Laborer	S	C	26	Georgia	June 10, 1920	4 yrs.	Penis, thigh	±	"Vigorous"	Curettment, cautery, roent. ray	+	38	9	Nearly healed; left AOR (at own risk).
3	J. J.†	♂	Laborer	M	C	28	Georgia	Jan. 3, 1920	4 mos.	Penis, groin	+	"Intensive"	0	+	70	12	Completely healed.
4	F. B.†	♂	Stevedore	M	C	27	Georgia	Sept. 5, 1920	3 "	Penis, groin, scrotum and perianal	−	0	0	+	42	6	Nearly healed on discharge. (Most of such patients were discharged, to return at stated time for follow-up treatments; few returned.)
5	M. N.†	♂	Laborer	S	C	32	Georgia	Sept. 23, 1920	1 mo.	Penis, scrotum	−	0	0	+	67	11	Elephantiasis of scrotum with subsequent gangrene; incision and drainage performed, later excision; patient died of sepsis following last procedure; lesions nearly healed at time of death.
6	J. F.	♂	Laborer	M	C	41	Florida	June 24, 1921	4 mos.	Groin, scrotum	−	0	0	+	60	8	Nearly healed on discharge; did not return for further treatment.
7	L. H.	♂	Laborer	S	C	29	New York	Mar. 5, 1922	4 "	Groin, scrotum, perianal	++	9 arsphenamin	0	0	74	11	Completely healed.

8	J. P.	♂	Porter	M	C	38	New York	Mar. 7, 1922	2 yrs.	Penis	−	10 arsphenamin	0	0	154	33	Completely healed.
9	E. V.	♂	Laborer	M	C	25	West Indies	Sept. 25, 1923	2½ "	Groins	−	0	18 T. E. (recur.)	+	0	0	Left AOR, refusing treatment; this patient had four relapses following apparent cures in a period of thirty months; tartar emetic used each time.
10	R. D.	♂	Laborer	S	W	42	Ireland	Feb. 6, 1925	1 yr.	Penis, groin	−	0	0	0	25	4	Nearly healed on discharge; did not return for follow-up treatment.
11	A. S.	♀	Housework	W	C	23	New Jersey	Sept. 16, 1925	4 yrs.	Labia, groin	++++	0	T. E., gr. v, t. i. w.	0	26	4	Patient had some treatment previous to admission; nearly healed on discharge.
12	M. L.	♂	Barber	S	C	39	New York	Jan. 25, 1926	16 mos.	Penis, prepuce	−	20 arsphenamin; Hg. ?x	10 T. E.	0	18	4	Appearance of lesions suggestive of syphilis, but unaffected by arsphenamin; nearly healed after tartar emetic; left AOR.
13	A. G.	♂	Porter	M	C	39	New York	Mar. 6, 1926	8 yrs.	Penis, scrotum	+	0	22 T. E. (recur.)	+	53	9	Scrotum and penis matted together by secondary cicatrization from previous lesions; separated by plastic operation, forming new penis; lesions cured.
14	W. W.	♂	Laborer	M	C	65	.....	May 16, 1926	2 "	Groin, scrotum, thigh	−	0	0	+	180	22	Nearly healed; went to another hospital.
15	M. G.	♀	Housework	S	C	26	New York	July 6, 1926	2½ "	Perineum, labia, vagina	−	0	Excision, 6 mo. before	0	23	6	Healing rapidly, but patient left AOR.
16	A. D.	♂	Sailor	M	C	23	Porto Rico	July 12, 1926	2 mos.	Penis, scrotum, groin	++++	"Intensive," 6 wks.	0	+	45	8	Onset ten days following venereal exposure; antiluetic treatment given elsewhere, but failed; nearly healed by tartar emetic; left AOR.
17	S. J.	♂	Laborer	S	C	35	New York	July 16, 1926	5 yrs.	Groin, scrotum	++++	0	T. E. 3 yrs. ago; amt. unknown	+	47	8	Nearly healed; patient a prisoner, transferred to another institution.
18	M. B.	♂	Tailor	S	C	31	Pennsylvania	Oct. 28, 1926	3 "	Groin	+	2 yrs.; amt. unknown	60 T. E. (recur.)	+	49	6	Nearly healed on discharge; previously treated with tartar emetic in Philadelphia, but suffered recurrence; did not return to follow-up clinic.

* Previously reported, Symmers and Frost, loc. cit.

† Previously reported, Campbell, M. F., loc. cit.

‡ Not looked for.

in the bacterial kingdom is uncertain. In many respects resembling the encapsulated bacillus of Friedländer, some have thought the two organisms identical[8] or closely related.[9]

FIG. 1.—Case VI. Typical case of granuloma inguinale showing well the multiplicity of lesions this disease may present. Involvement of penis, groin and scrotum with a narrow band of infection extending to perineum on left side.

FIG. 2.—Case XIII. Marked scarring from previous granuloma infection with matting together of penis and scrotum in firm cicatrix. Active lesions below. The deformity was relieved by plastic operation with satisfactory penile reconstruction.

The derivation of this particular organism is uncertain. Donovan believed the germ to be a protozoön; Flu,[10] a chlamydozoön; Siebert,[11] an encapsulated diplococcus; Aragao and Vianna,[12] a separate genus of schizomycetes, called by them calymmatobacterium granulo-

matis. The reciprocal identity of the organism seen in smears and that obtained by culture may be justifiably questioned. It is pointed

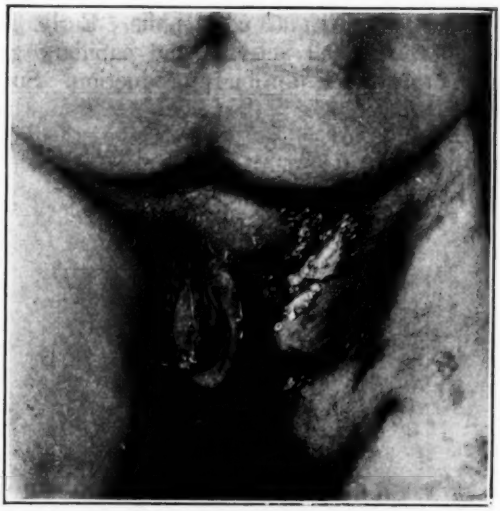

FIG. 3.—Case XIV. In this patient, aged sixty-five years, the granulomatous element predominates. Donovan bodies found. Healing progressed rapidly with tartar emetic.

FIG. 4.—Case XV. Small lesions about lower labial angle with moderate-sized granulomatous ulceration in lower vagina. It is interesting to note that a similar lesion had been excised six months previously with prompt recurrence. Thought to be epithelioma, the histologic picture was that of a granuloma. Healing progressed rapidly under tartar emetic therapy.

out by Jones and Gage[13] that "If granuloma is a bacterial disease, then we would possess the first synthetic drug (antimony potassium tartrate) against vegetable parasites in the history of medicine."

Numerous descriptions to the contrary notwithstanding, we believe there is nothing peculiarly characteristic or diagnostic in the histologic picture. There is a marked round-cell infiltration with myriads of plasma cells and eosinophils. Early lesions show increase in endothelial cell activity and capillary growth while older lesions contain much fibroblast production. Surface epithelium is thin and delicate or if lost by ulceration, the superficial portions of the tissue show the picture characteristic of inflammatory reaction with marked polymorphonuclear invasion. Absence of giant cells and caseation is noteworthy. In short, the picture is not unlike that of a simple granulomatous process.

FIG. 5.—Case XVI. Lesion regarded as luetic elsewhere and treated by vigorous antiluetic therapy without benefit disclosed Donovan bodies and was nearly healed after eight antimony injections.

Tartar emetic (potassium antimony tartrate) intravenously (1 per cent solution) is a specific remedy. This may be given in amounts as high as 20 cc., although such a dose may produce emesis, a variable shock reaction or marked regional pains, particularly in the shoulder joints. At Bellevue, where we[14] were the first to treat this condition in the United States with tartar emetic, our usual practice has been to start with 2 cc. of the 1 per cent solution intravenously, increasing the dosage 1 cc. every other day. Rarely have we given more than 10 cc. at one time. Improvement in the lesion is quite as immediate, striking, and rapid as are changes in superficial luetic manifestations following arsphenamin. It is

advised that injections be continued for some time after the apparent cure of the disease. We have seen a relapse in 4 cases in which treatment was discontinued with the superficial healing of the lesion. A tabulated summary of 18 cases observed in Bellevue is herewith presented.

FIG. 6.—Case XVII. Lesion of five years' duration. Nonpigmented scarring following tartar emetic treatment three years ago in right groin. Recurrence below and on left side.

Bacteriologic and Experimental Studies. The observation on which McIntosh bases his conclusions as to the etiologic specificity of this organism follows briefly: Tissue excised from an active lesion of granuloma inguinale was transplanted to another human with subsequent development of the disease at site of inoculation in the new host. The Donovan bodies of granuloma inguinale were recovered from the new lesion. While these organisms may very probably cause the disease, tissue transplantation *en masse* absolutely precludes a conclusion as to the specificity of an organism according to the postulates of Koch—for it is conceivable that another organism not recoverable by the methods used may have been transplanted.

For the isolation of the Donovan bodies, Sabouraud's medium (4 per cent maltose peptone agar) is essential. When once isolated, these organisms are found to grow well on the more common laboratory media and our observations on the cultural characteristics

are quite in harmony with those of other observers. Colonies on Sabouraud's medium are sharply demarcated, round, domelike and have a diameter of 0.5 to 3 mm. When young, they are translucent but become opaque after one day. They will grow anaërobically as well as aërobically. Good growth is obtained on agar (blood and nutrient), blood serum and gelatin, without liquefaction in the latter. Blood is not hemolyzed.

Plain and glucose bouillon becomes cloudy in twenty-four hours with subsequent sedimentation and without pedicle formation.

Lactose, maltose, levulose, dextrose, saccharose, and galactose are acidified without gas production. Indol is not produced on inulin.

Morphologically, these organisms in cultures range in size from 1 to 5 micra, the smallest appearing as cocci, the largest ovoid or oblong. Marked pleomorphism is characteristic; spores are not formed; motility is absent. A capsule is demonstrable in direct smears from the lesions but this disappears in subcultures.

Having isolated the organism, the cultural characteristics of which have just been described and the morphology of which seems identical with the so-called Donovan bodies, inoculation experiments were carried out on guinea pigs, rabbits, monkey, and humans. All inoculations were made in the following manner: On the right side subcutaneous injections (0.5 cc. suspension twenty-four-hour growth) were made at: (1) Pubis near midline; (2) midinguinal region; (3) upper lateral groin; (4) inner thigh; (5) lower abdomen. At corresponding points on the left side scarification inoculations were made. All were protected and observed for two months save two guinea pigs which died of other causes as did one human (carcinoma).

Guinea Pigs. Six animals were injected. No reaction other than localized abscess formation was observed on the right side and this was not noted at each site of inoculation. No lesions comparable in any manner to granuloma inguinale developed on either side in two months. The organisms were recovered from the abscess formation in two instances after one week.

Rabbits. Three rabbits were injected in similar manner, developing localized subcutaneous abscesses but no lesions suggestive of granuloma inguinale.

Monkey. One animal (Macaccus rhesus) failed to develop other than localized abscesses during a period of six weeks' observation. The organisms were recovered from an abscess in this animal after six days.

Human. Having obtained negative results with the organisms thus far, organisms were isolated from our next admission (Case VI) and 3 guinea pigs, and 3 humans were injected. No granuloma lesions developed in the animals. The purpose of the observations were explained to the human subjects and with assurance that should the inoculation "take" cure could be readily obtained, full consent was granted for the procedure. The first

two were colored, one a man, aged sixty-two years, with inoperable carcinoma, one a young adult, aged twenty-six years, with chancroidal bubo. One week later, emboldened by the negative results thus far obtained, the writer inoculated himself in a similar manner. Save for the appearance of small localized abscess areas at site of subcutaneous inoculation, no disease developed in any case. In none of the experiments did more than transient superficial inflammatory reaction occur at site of scarification inoculation. The patient with carcinoma was transferred to another institution where he died six weeks later but we had opportunity of observing him there. No lesions developed.

Summary. Granuloma inguinale is a clinical entity rapidly acquiring more general recognition and a literature of its own.

It is found chiefly among negroes, particularly those from the Southern States.

While affecting the genital and perigenital tissues chiefly, it is no ta venereal disease; transmission by sexual intercourse has not been observed.

The etiology is indefinite, for while the intracellular inclusions described by Donovan seem to bear a direct relationship to the disease and are found with striking constancy, the disease has never been experimentally produced by the injection of these organisms (or what is considered morphologically and culturally to be these organisms) alone.

Experimentally, we have obtained uniformly negative results in the reproduction of the disease by bacterial injection. To date, Koch's postulates have not been specifically fulfilled.

Tartar emetic intravenously constitutes a specific treatment.

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THE SEDIMENTATION REACTION IN CANCER.

By E. H. Rubin, M.D.,
NEW YORK.

(From the Cancer Service and the Radiotherapy Department of the Montefiore Hospital, New York.)

An increase in the rate of sedimentation of erythrocytes has been observed in a variety of diseases including tuberculosis, cancer, syphilis, in acute infections and surgical conditions. Yet in spite of its nonspecificity, the test has been utilized as a diagnostic and prognostic aid. Our own experience with the test in approximately 500 cases during the past three years has convinced us that the test possesses considerable value if the results are correlated with the remainder of the clinical picture and if its limitations are kept in mind. The latter phase of the problem, however, deserves more attention than has been generally given to it and the purpose of this paper is to emphasize those conditions that render the interpretation of the results difficult and also to enlarge on several incidental findings that increase the usefulness of the test.

Material. The study comprised 127 patients with malignant tumors and 26 healthy controls. The clinical diagnosis was confirmed on 119 of the patients either by autopsy, biopsy, at operation, roentgenologically or by endoscopic visualization. The remainder include those with cutaneous involvement or patients in whom the clinical course and final outcome made the diagnosis fairly certain. Whenever possible, the tests were repeated at monthly intervals. In all, 237 tests were done. The majority of the cancer cases were in advanced stages of the disease but a number of relatively early cases were also studied in the Radium Clinic of the Montefiore Hospital.

Method. The method used was that recommended by Morriss.[1] The test was done as follows: Into a 2-cc. Record syringe, a solution of 3.8 per cent sodium citrate was drawn to the 0.4 mark. Blood was then aspirated from an arm vein with a minimum of stasis to the 2-cc. mark, giving a dilution of 1 to 4. The blood was poured into small tubes such as are used in the Wassermann test and mixed gently by inverting the tubes several times. The blood was then drawn into 1-cc. serologic pipets, graduated into hundredths and then placed in a suitable stand and the layer of clear plasma observed at the end of one, two and twenty-four hours. The results were read directly in volumes per cent. The height of the blood column ranged between 19 and 21 cm. The two-hour reading being the most significant, is the one given in the tables.

Normal Standards. The sedimentation reaction was done on 26 physicians, medical students and nurses to determine the limits of normality. It is seen in the accompanying table that with few exceptions, the two-hour readings were found to be in agreement with

those obtained by Morriss on his 21 healthy controls—up to 5 per cent for men and up to 10 per cent for women. In several instances, however, the readings were higher in our series but in no case did they exceed 15 per cent. To allow for such discrepancies as well as for a certain margin of error, the rate of sedimentation was not considered abnormal unless the two-hour reading was 20 per cent or over. Normal sedimentation readings were also obtained in patients with chronic constipation, dislocations, uncomplicated herniæ, benign prostatic adenomata and in several neurologic conditions such as benign tumors of the hypophysis, postencephalitic Parkinson's disease, multiple sclerosis and hemiplegias following intracranial hemorrhage.

TABLE I.—NORMAL TWO-HOUR SEDIMENTATION PER CENT.

	No.	1 to 3 per cent.	3 to 5 per cent.	5 to 7 per cent.	7 to 9 per cent.	9 to 11 per cent.	11 to 13 per cent.	13 to 15 per cent.	Over 15 per cent.
Men	16	9	2	2	2	0	1	0	0
Women . . .	10	0	0	2	3	3	1	1	0
Total . . .	26	9	2	4	5	3	2	1	0

Results. The two-hour sedimentation values obtained at the last determination are recorded in the following table:

TABLE II.—TWO-HOUR SEDIMENTATION PER CENT IN CANCER PATIENTS.*

Group.	No.	Diagnosis.	1 to 10 per cent.	10 to 15 per cent.	15 to 20 per cent.	20 to 30 per cent.	30 to 40 per cent.	40 to 50 per cent.	50 to 60 per cent.	60 to 70 per cent.	70 to 80 per cent.	80 to 90 per cent.	90 to 100 per cent.
1 . .	20	Cancer of breast	..	..	..	..	3	5	6	5	..	1	
2 . .	10	Cancer of esophagus	..	1	..	..	3	1	2	3			
3 . .	18	Cancer of stomach*	..	..	..	5	1	4	4	2			
4 . .	9	Cancer of colon*	..	..	..	2	1	3	1	1			
5 . .	8	Cancer of rectum and anus	..	1	1	..	1	1	2	1	..	1	
6 . .	8	Cancer of larynx and lungs	..	..	..	1	4	1	..	2			
7 . .	10	Cancer of kidney and bladder	..	..	..	2	..	2	3	1	2		
8 . .	14	Cancer of abdominal organs*	..	..	..	1	3	4	2	3			
9 . .	10	Cancer of skin	..	..	..	4	..	1	2	3			
10 . .	7	Sarcomata	..	..	1	..	..	1	3	1	..	1	
11 . .	13	Miscellaneous	..	..	..	1	4	3	3	2			
Total	127	.....	..	2	2	16	20	26	28	24	2	3	

* In 4 patients the two-hour reading was unobtainable because the border was diffuse.

Group 1. Cancer of the breast gave an increased sedimentation rate. No readings within normal limits were obtained. A careful study of individual cases showed that the rate of sedimentation increased with the spread of the tumor, but even more so with the toxic action of the cancer on the body as evidenced by increasing weakness, anemia, loss of weight, body pains and occasionally fever. Patients with skeletal and pulmonary metastases gave exceptionally high readings. The temperature charts were of no particular significance but the rate of sedimentation appeared to be a good indication of the patient's condition. Ambulatory patients showed moderate increases in the rate of sedimentation which became more marked as the disease progressed as illustrated in the following case:

K. B., aged forty-four years, had cancer of the breast with skeletal metastases.

February 8, 1926: 25 per cent; ambulatory.
May 21: 37 per cent; ambulatory.
June 22: 45 per cent; ambulatory.
July 19: 50 per cent; in wheel chair.
August 5: 52 per cent; in wheel chair.
October 7: 52 per cent; in wheel chair.
November 11: 59 per cent; in bed, occasionally in wheel chair.
March 15, 1927: died.

Patients in more advanced stages of the disease gave higher readings with slight fluctuations from time to time.

D. P., aged thirty-seven years, had cancer of the breast with skeletal metastases.

February 3, 1926: 49 per cent; in wheel chair.
March 23: 55 per cent; in wheel chair.
May 21: 62 per cent; in wheel chair.
June 9: 62 per cent; bedridden.
July 19: 50 per cent; bedridden.
August 5: 60 per cent; bedridden.
September 1: 62 per cent; bedridden.
September 16: died.

In patients in whom the disease had assumed a rapid and fulminating course, the rate of sedimentation was extremely rapid.

L. G., aged forty-eight years, had cancer of the breast with skeletal and orbital metastases.

May 30, 1926: 75 per cent; bedridden.
June 22: 78 per cent; bedridden.
July 19: 83 per cent; bedridden.
August 3: died.

Group 2. Similar results were obtained with cancer of the esophagus. One patient with early cancer of the esophagus but otherwise in good physical condition had a normal sedimentation rate. He left the hospital after a diagnosis was made and went back to work, but at the end of eleven months he had to return to the hospital where he died a short time later. This case as well as several others which will be referred to later bore out our previous interpretation of the test,[2] namely, that cancer in an early stage need not cause an increase in the rate of sedimentation. The assertion of Gueissaz[3] that a normal sedimentation rate excludes with certainty a malignant neoplasm is, therefore, unwarranted. Furthermore, it does not appear that the test can be relied upon to determine postoperative residue as has been advocated by several investigators.[4]

In a patient with cancer of the rectum, there was obtained seven months after radical removal of the growth a sedimentation reading of 13 per cent, a normal rate of sedimentation in spite of gross and microscopic evidence of recurrence. The patient was able to do her usual housework but had to be readmitted one year after her first operation for a palliative colostomy. The sedimentation reaction at this time was 52 per cent.

It has been claimed by several authors[5] that the sedimentation test can be used in the differential diagnosis of malignant disease and nonmalignant conditions of the esophagus such as polypi, multiple diverticula and cardiospasm. Our results do not confirm these findings. In evaluating the test in malignancy of the esophagus, another factor must be considered, namely, the possibility of increased blood concentration in this condition. Master[6] found an increased blood concentration as evidenced by increased cell counts in patients with cancer of the esophagus. The occurrence of an increased cell volume in cancer of the esophagus would undoubtedly tend to delay the rate of sedimentation.

Group 3. An increased rate of sedimentation was also found in patients with cancer of the stomach. Of special interest was the occurrence of slight increases in the sedimentation rate (20 to 30 per cent) in 5 patients who had considerable carcinomatous involvement of the stomach. Stemmler[7] observed two such cases. He interpreted his results on the assumption that cancer of the stomach had little tendency toward disintegration in spite of massive infiltration into the surrounding tissues and that, therefore, the sedimentation rate was little affected.

Although the sedimentation rate, as a rule, was more pronounced in cases having ulcerating tumors, the occurrence of a slightly accelerated rate could not be attributed solely to the absence of disintegration. We compared the sedimentation rates with the autopsy findings on 20 patients which included 1 of the 5 cases referred to above, and we were unable to observe any relationship

between the rate of erythrocyte sedimentation and the presence or absence of tissue disintegration. Several patients with extensive tumor formation and necrosis gave during life moderate acceleration in their sedimentation rates. On the other hand, a number of patients with nonulcerating tumors gave high rates.

The sedimentation rates were related to a greater degree to the rapidity of progression and the severity of a disease process and the constitutional reaction of the patient. A rapidly progressive course was associated with the greatest increase in the sedimentation rate, providing death did not intervene because of intercurrent complications. In such instances, however, the reaction may be of considerable diagnostic value as to the mode of death. This phase of the problem will be discussed more fully later. A disease characterized by a protracted and slowly progressive course caused a slow and steady increase in the sedimentation rate which after reaching certain limits had a tendency to vacillate from time to time, until death supervened. When such patients reached a stage of cachexia, the reaction occasionally showed a tendency to approach the normal. The cause of this is not quite clear but it has been observed also by Westergren[8] in cachectic stages of tuberculosis. Such cases were not frequent since death usually supervened before that stage was reached. In our series, one patient with rib sarcoma and another with cancer of the rectum, gave two-hour readings of 19 and 15 per cent respectively. Both patients were extremely cachectic and on postmortem examination revealed extensive metastases. The following patients exemplify the other types of reactions:

A. M., aged forty-eight years, had metastatic cancer involving the skeletal system. The course was rapidly progressive.

May 19, 1926: 42 per cent; bedridden.
June 20: 50 per cent; bedridden.
July 28: 69 per cent; bedridden.
August 2: died.

E. K., aged, sixty-five years, had cancer of the upper lip with necrosis of the jaw bone. The course was slowly progressive.

February 3, 1926: 54 per cent; ambulatory.
March 22: 48 per cent; ambulatory.
May 21: 47 per cent; ambulatory.
June 9: 64.5 per cent; ambulatory.
July 13: 62 per cent; ambulatory.
August 5: 62 per cent; ambulatory.
August 31: 52 per cent; ambulatory.
October 7: 57 per cent; ambulatory.
November 11: 50 per cent; ambulatory.
May 21, 1927: died.

S. S., aged seventy-three years, had cancer of the stomach with skeletal metastases. The course was slowly progressive with increasing cachexia.

February 8, 1926: 49 per cent; bedridden.
May 21: 48 per cent; bedridden.
June 9: 53 per cent; bedridden.
July 13: 59.5 per cent; bedridden.
August 5: 61 per cent; bedridden.
September 1: 57 per cent; bedridden.
October 7: 45 per cent; bedridden.
October 21: died.

A number of investigators have advocated the sedimentation reaction in the differential diagnosis of cancer and ulcer of the stomach. But because of the nonspecificity of the test and the frequency of finding an accelerated sedimentation rate in ulcer and a slightly increased or even normal rate in early cancer, such use of the test is fraught with error. Occasionally, repeated tests may be of confirmatory value in clearing up a doubtful case as illustrated in the following:

S. F., aged fifty-two years, was admitted with a diagnosis of cancer of the stomach. Roentgen ray examination was negative. In the hospital, he was ambulant, afebrile and gained in weight and strength. The final diagnosis on discharge was that of a healing gastric ulcer.

February 19, 1926: 31 per cent; ambulatory.
March 2: 22 per cent; ambulatory.
April 8: 15 per cent; ambulatory.
May 20: 12.5 per cent; ambulatory.
June 3: discharged improved.

The continued tendency of the sedimentation rate to approach normal limits while, at the same time, the patient was showing clinically signs of improvement, supported the final diagnosis of healing gastric ulcer rather than the admission diagnosis of cancer.

Group 4. What has been stated regarding cancer of the stomach applies equally to cancer of the lower intestinal tract, of the thoracic and abdominal viscera, Hodgkin's disease and sarcomata. Cancer of the skin in its early and localized stages gave a slight increase in the sedimentation rate. With the extension of the process and the involvement of subcutaneous tissues and bone, the reaction became more accelerated. Successful surgical removal of an early skin cancer in one patient caused the rate of sedimentation to return to normal limits. Such a finding, however, should not be taken as absolute evidence of cure unless the test remains persistently within

normal limits for a considerable length of time and is corroborated by clinical observation.

J. F. aged thirty-seven years, had cancer of the face.
November 25, 1924: 21 per cent.
December 1: 43.5 per cent; two days after operation.
February 27, 1925: 11.5 per cent.
March 18: 8 per cent; discharged cured.

Diagnostic Value. The diagnostic value of the sedimentation reaction is secondary to its importance in indicating the clinical condition of a patient and the severity of the disease. In spite of the infrequency of normal sedimentation rates in cancer, the test appears to be of little value in differential diagnosis. Chronic wasting diseases, acute infections, disturbances in metabolism, acute and chronic surgical conditions and even physiologic changes such as menstruation and pregnancy influence the rate of blood sedimentation. In incipient disease and where the diagnosis is most difficult, the rate of sedimentation may be normal. A normal rate is, therefore, of little value but an increased rate definitely indicates some organic disturbance when physiologic factors are excluded. The ability of the test in indicating the acuteness and severity of an infection has been utilized with considerable success in surgery and gynecology.[9] The test is used in these fields to determine the advisability of, and the time for, operative procedure. The value of the test in other medical and surgical conditions has been reviewed elsewhere.[10]

Prognostic Value. In prognosis, repeated tests are of considerable value. Our observations in other diseases have shown that with improvement, the rate of sedimentation tends to approach normal limits. This was seen in several patients with tuberculosis upon whom successful pneumothorax or thoracoplastic operations had been performed as well as upon a number of patients with improved or cured surgical conditions. On the other hand, the fatal evolution of a disease is almost invariably accompanied by an increased rate of sedimentation as was demonstrated previously.

It was mentioned previously that when death occurred in cases in which the sedimentation rate had shown only slight or moderate increases, such readings might furnish a clue as to the mode of death. A careful study of 70 patients who died during the period of observation revealed the fact that very frequently when patients died in the relatively earlier stages of the disease and had consequently shown little change in the sedimentation rate, death was sudden and the result of an accident or a complication such as an internal hemorrhage, embolism, intestinal obstruction or following surgical procedures. On the other hand, when patients had shown increased sedimentation rates during life, death was apparently the result of the natural evolution of the disease, or at any rate, not due

to any demonstrable complication or accident. It may be assumed that in the former group, the disease had not progressed sufficiently to cause the increases in the sedimentation rate that were observed in the latter group.

Concurrent Observations. At the end of twenty-four hours, the blood in the sedimentation pipettes differentiates itself into three distinct layers: plasma, white blood cells and red blood cells. Like the sedimentation test, these layers have certain features of practical as well as historical interest. The appearance of the serum has been used to determine the bilirubin content of the blood long before quantitative tests were adopted. Fishberg[11] has only recently directed attention to the diagnostic value of the visual appearance of the blood serum in pernicious and secondary anemias; the serum being more deeply pigmented in the former. We have found several cancer patients whose plasma showed a distinct yellowish tinge and upon examination by van den Bergh's method revealed an increase in the content of the bilirubin. These patients were suspected clinically of having liver metastases. Roessingh[12] found an increase in the bilirubin content of the serum in 7 of 70 cases of carcinoma in all of whom liver metastases were present. But the fact remains that a patient may have liver metastases without changes in the bilirubin content of the blood. The location of the metastatic nodules and their relation to the biliary system may therefore be of deciding importance. Of the 20 patients that were examined post-mortem, metastatic nodules in the liver were found in 9, but only 2 patients had shown any appreciable increase in the color of the plasma during life. The finding of an increased bilirubin content in cancer is probably a reliable indication of the existence of metastases in the liver or biliary system but the absence of color changes does not exclude it.

The height of the white and red blood-cell layers was found to be roughtly proportional to their respective cell volumes. In patients with leukocytosis, the white-cell layer was noticeably increased in height. In several tabetic patients in whom malarial organisms were artificially inoculated, the white-cell layer was quite thin. These patients had the characteristic leukopenia of malaria. The differences in the height of the white-cell layer are easily perceived when several pipettes are set up simultaneously.

With regard to the height of the red-cell layer, our earlier comparisons between their number and the twenty-four-hour reading failed to reveal any definite relationship. Later experiments showed quite conclusively that the height of the red-cell layer at the end of twenty-four hours, at which period sedimentation is practically completed, was directly proportional to the cell volume as determined by the hematocrit. We have shown this relationship by using hirudin as an anticoagulant, which obviated certain errors inherent in the methods that employ salts or diluents to prevent coagulation.[13]

The spontaneous settling of the erythrocytes and leukocytes has been utilized long ago for the determination of their respective cell volumes. Mosler[14] advocated this method in 1872 in leukemia and Marcano[15] described in 1901 a microsedimeter for the determination of red cell volume. Incidentally, Marcano's instrument was also advocated by the author to determine the sedimentation rate of erythrocytes, a method of investigation that had been recommended by Biernacki[16] three years previously.

We agree with Engel[17] that the hazy and washed-out border that is seen in rapidly sedimenting blood is not due primarily to the high degree of anemia which is always present in these cases but rather to certain factors in the suspension medium. We have tested blood with cell volumes as low as 19 per cent, and yet, at the second hour, the cell border was quite sharply delineated. On the other hand, we have had several samples of blood whose cell volume was greater and yet the upper cell border was so uneven and hazy that an accurate reading could not be taken at the end of the second hour. Repeated tests gave similar results.

Causative Factors. The explanation of the erythrocyte sedimentation reaction has engaged the attention of a number of investigators. One group[18] believes that the reaction is primarily an agglutination phenomenon of an electrical nature in which positively charged bodies in the plasma are attracted by negatively charged erythrocytes thereby bringing about a diminution in the suspension stability of the latter. Frisch and Starlinger[19] emphasize the importance of the fibrinogen content of the blood in causing acceleration in the rate of sedimentation. Studies by others[20] have shown the globulin-albumin ratio of the blood to be increased toward the globulin side and that this paralleled the rate of sedimentation. Others have noted changes in the content of total proteins, cholesterin, lecithin, lipase and phosphorous and in the viscosity and surface tension of the serum as well as alterations in the size, number and hemoglobin content of the erythrocytes. Ponder[21] has latterly interested himself in the hydrodynamics of the reaction. His work is of fundamental importance and offers to clear up a phase of the problem that is little understood.

In spite of apparent differences of opinion regarding the cause of the velocity of sedimentation of the erythrocytes, a closer study of the problem reveals a certain relationship between the various factors which would lead one to assume that although no single component of the blood can be held directly responsible for the phenomenon, all the physicochemical changes enumerated above are in some manner intimately related. The degree and manner with which each factor is implicated is probably determined by the nature, location and severity of the disease process.

For example, Duzár[22] found that in tuberculous children there is at first seen an increase in globulin, in later stages, an increase in

fibrinogen and in the severest cases there is a high globulin and fibrinogen content in the blood. Moreover, it is well known that certain diseases are associated with high fibrinogen values while in others the globulin fraction is greatly increased.[23] A high globulin content in the serum is related to an increase in its viscosity[24] and a decrease in its surface tension. Both fibrinogen and globulin in concentrations above normal increase the power of precipitation of the plasma or serum[25] and we have observed that the plasma or serum showed increasing ability of precipitation[26] and the cells, a diminution in volume in almost direct proportion to the increase in the rate of erythrocyte sedimentation.[27] It is evident from a study of these interrelated facts that the sedimentaton test is not explained through the agency of any single component or factor in the blood but that it is rather the expression of an alteration in the entire blood structure that accompanies disease.

The changes in the properties of the blood that have been mentioned are found to a greater or lesser degree in all disease conditions in which increased sedimentation rates have been noted. On the basis of these nonspecific changes, a number of tests have been advocated for the diagnosis of cancer, tuberculosis and syphilis which later study proved unreliable. Use has been made in these tests of chemical precipitants, the absorptive power of the serum proteins for various dyes and the physical properties of the serum. The details of these tests do not concern us here.

It must be emphasized that the erythrocyte sedimentation reaction is similarly a nonspecific phenomenon and the clinical value of the test will largely depend upon a knowledge of its limitations.

Summary. The erythrocyte sedimentation reaction was studied on 127 patients with various forms of malignant tumors and in various stages of the disease. The rapidity of erythrocyte sedimentation was found to parallel the extent of the disease and the condition of the patient. In this respect it afforded a better guide to the condition of the patient than the temperature chart. Repeated examinations revealed the fact that the progress of the disease was invariably accompanied by an increasing rapidity of erythrocyte sedimentation. However, cachexia tended to decrease the rate. The test was found to have little value in differential diagnosis because of its nonspecificity and because early cancerous growths produced relatively little alteration in sedimentation velocity. Yet, strictly normal sedimentation values were extremely infrequent in the presence of definitely diagnosed cancer. It was also noted that in cases where death occurred early in the disease when the sedimentation velocities were only moderately accelerated, the former could be traced to an accident or complication, such as a fatal hemorrhage, embolism or following surgical procedures. When the disease ran an acute course, the velocity of erythrocyte sedimentation was greater than in cases pursuing a more chronic

course. Although the rapidity of erythrocyte sedimentation in cancer patients is to a great extent determined by physicochemical changes in the plasma, it must be emphasized that the increasing anemia of these patients is an additional factor, contributing to the rapidity of erythrocyte sedimentation in these cases.

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FAMILIAL EPISTAXIS WITHOUT TELANGIECTASIA.*

By Herbert Z. Giffin, M.D.,
ROCHESTER, MINN.

A review of cases of hemorrhagic disease including epistaxis that have been observed at the Mayo Clinic during the last five years indicates that besides the blood dyscrasias, epistaxis may result from the following conditions: Traumatic ulcer, dilated vessels, local telangiectasia, local purpuric and petechial areas, deflected septum, osteoma of the antrum, abscess of the floor of the nose, sinusitis, syphilitic ulcer of the nose, hypertension and cardiovascu-

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lar disease, sudden changes in atmospheric pressure, and cases in which the metabolic rate is low. Not infrequently a local condition and blood dyscrasia coëxist, and the presence of a possible local cause of epistaxis, therefore, does not exclude the presence also of hemorrhagic disease.

Legg (1876), Chiari (1887), Rendu (1896), and Osler (1901) reported early cases of familial epistaxis associated with telangiectasia. This condition is now generally recognized. It should be noted here that there is also a form of familial epistaxis without telangiectasia and that this syndrome may represent a form of purpura.

Lane (1917) reported on a family in which thirteen members in three generations had experienced epistaxis during adolescence only, the epistaxis ceasing entirely after the age of eighteen or twenty years. There was no evidence of hemophilia in the clinical history of these cases, and the blood coagulated normally. It is not definitely stated, however, that telangiectasia was absent but the cessation of epistaxis after adolescence would make its presence improbable. Familial adolescent epistaxis without telangiectasia is evidently unique.

Goldstein (1922) suggested the existence of cases of familial epistaxis without lesions of the skin but in the cases he described it was not clear whether telangiectatic areas were absent.

Blumenfeld (1926) under the title of "Familial Epistaxis" described the only clear-cut case of familial epistaxis without telangiectasia which is not confined to the adolescent period that I was able to find reported in the literature. The patient was a man aged forty-five years, who had suffered from recurrent epistaxis since childhood. Two brothers, two sisters, and four of his children also suffered from recurrent epistaxis. Anemia was severe; the platelet count was 104,000, bleeding time and coagulation time were normal. The patient bled from both sides of the nose and no ulceration or telangiectasia could be demonstrated.

Case Reports. Four cases of familial epistaxis without telangiectasia which have come under my observation are herewith summarized:

Case I.—A single woman, aged thirty-one years, came to the Mayo Clinic in 1915. She had had epistaxis since childhood with exacerbations at intervals, when bleeding might occur several times a day. She came again in 1923 at the age of thirty-nine years, during one of her periods of excessive epistaxis. No other bleeding had occurred but menstruation had been somewhat profuse. The blood count showed slight secondary anemia; the differential count was negative. A careful search for telangiectasia was made but this could not be found. Examination of the nose showed atrophic areas with submucous hemorrhages like those seen with purpura. The paternal grandmother, the father, one sister, and two brothers had had epistaxis (Fig. 1).

The patient was under observation for three months during which time coagulation factors were carefully studied. Of seventeen estimations of the

platelet count by the citrate method, twelve were below 150,000 and four of these approximated 100,000. Coagulation time by the Boggs method, and bleeding time and coagulation time by the Lee and White method, and calcium time, and estimations of the prothrombin time, were normal. Clot retraction was satisfactory. The tourniquet test was slightly positive. At one time pin-point submucous hemorrhages were present in the mouth. A study of the nail-fold capillaries demonstrated that they were fine and tortuous and that the flow was uniformly slow. The spleen was not palpable and other observations were not significant. Coagulants caused temporary improvement, but a recent report states that permanent relief was not effected.

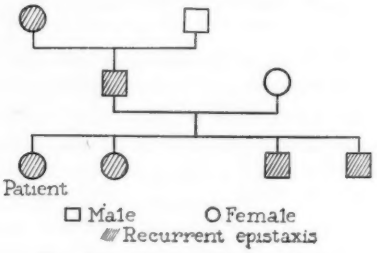

FIG. 1.—Case I. Heredity chart.

CASE II.—A man, aged twenty-six years, came under my observation in 1924. He had had frequent severe nosebleed since childhood; the bleeding was excessive for six or eight weeks each year during the spring and summer. The mother, the mother's brother, two brothers and three sisters had suffered from frequent epistaxis (Fig. 2).

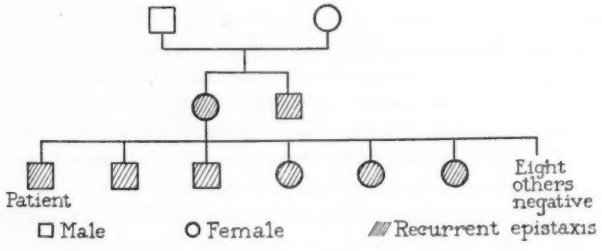

FIG. 2.—Case II. Heredity chart.

The blood count, including the differential, was negative at the time of examination. The platelet count was 110,000, the coagulation time by the Boggs method was normal, and the bleeding time was slightly prolonged (four minutes). Coagulation time by the Lee and White method, calcium time, and prothrombin time were normal. The tourniquet test was negative. There was no evidence of telangiectasia in the nose, throat or elsewhere. The mucous membrane appeared to be thin and a traumatic ulcer was present on the right side of the septum. It was felt, however, that the local condition was not sufficient to account for such severe recurrent epistaxis, nor would this explanation be consistent with the familial character of the condition. The spleen was not palpable and the history was not indicative of hemophilia.

CASE III.—A man, aged thirty-six years, came under my observation in 1925. He had had periodic epistaxis since childhood; occasionally the bleeding occurred from two to five times a day and lasted for from ten to thirty minutes. A paternal grandmother, two paternal great uncles, a paternal aunt, two paternal uncles, the father, and two half-sisters all had suffered from severe epistaxis. In two members of the family, epistaxis had been regarded as at least a contributory cause of death. There was also a history of migrain in the family (Fig. 3).

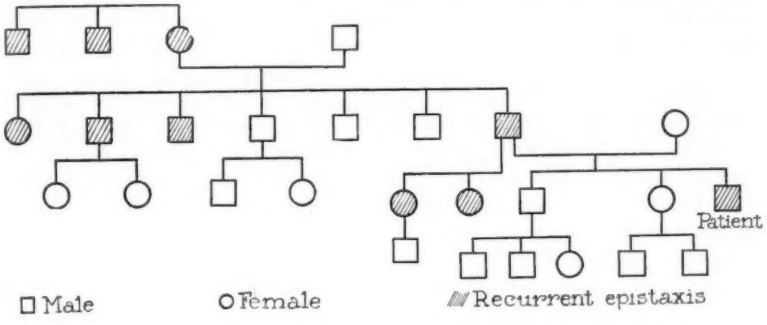

FIG. 3.—Case III. Heredity chart.

At the time of observation the patient was markedly anemic. The hemoglobin was 36 per cent (Dare), erythrocytes numbered 2,950,000 and the leukocytes 6400; the differential count was negative. The platelet level was definitely low, varying from 76,000 to 128,000 on seven counts. Coagulation time by the Boggs method, and bleeding time and coagulation time by the Lee and White method and calcium time, and prothrombin time were normal, and clot retraction was complete at the end of two hours. The tourniquet test was slightly positive. The spleen was barely palpable. A study of the nail-fold capillaries did not show abnormalities. Examination of the nose and throat revealed buried and injected capillaries on the inferior turbinates. These did not definitely represent telangiectasia, and telangiectasia was not found elsewhere on the body. Petechiæ were present on the roof of the mouth and the upper lip.

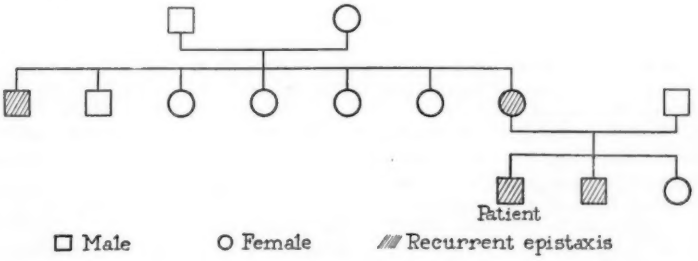

FIG. 4.—Case IV.—Heredity chart.

CASE IV.—A man, aged twenty-eight years, came under my observation in 1925. He had had epistaxis since childhood, the attacks recurring every two or three months and lasting intermittently for from one to two

weeks. During the two years preceding examination the attacks had become more severe. There was no history of other bleeding. A maternal uncle, the mother, and a brother had epistaxis (Fig. 4). A curious incidental feature of the family history was the fact that the maternal grandfather, two uncles, and the mother had polycystic disease.

A careful search for telangiectasia in the nose and throat and elsewhere was negative. The platelet level was somewhat low, three of four counts being less than 118,000. The coagulation time by the Boggs method, and bleeding time and coagulation time by the Lee and White method, and calcium time and prothrombin time were normal. Clot retraction was complete in three hours. The tourniquet test was negative. The spleen was not palpable.

Comment on Cases I to IV. These cases of familial epistaxis without telangiectasia have occurred in both men and women and the heredity has been both maternal and pateral. Although there are not sufficient data with respect to the family histories to prove that the heredity follows the mendelian law, the epistaxis does not appear to be a recessive characteristic. While generalized purpura was not present in any of the cases, petechiæ were found in the mouth in 1 case and purpuric areas in the nose in another. The 4 cases show one striking feature in common: a somewhat reduced platelet level on repeated counts. All other features of coagulation were essentially normal. In contrast to this, my own cases of familial epistaxis with telangiectasia have shown a normal platelet level. These facts suggest quite definitely that the condition is not hemophilic, and may be purpuric.

Two well-marked cases of recurrent epistaxis without telangiectasia but without a family history of epistaxis have been noted.

CASE V.—A man, aged twenty years, had had nosebleed at least once a month for the preceding three years. The platelet level was definitely low, the bleeding time was slightly prolonged, and coagulation time by the Boggs method, coagulation time by the Lee and White method, and calcium time were normal. Retractility of the clot was not estimated. Examination of the nose and throat was negative aside from the presence of infected tonsils. Following tonsillectomy the bleeding improved although it still recurs on exertion in hot weather.

CASE VI.—A man, aged thirty-seven years, had had epistaxis since the age of seven years. It had occurred two or three times a month and sometimes lasted two or three days. The patient bruised rather easily, but did not bleed from the gums or elsewhere. The platelet level was definitely low and the bleeding time somewhat prolonged, but coagulation time by the Boggs method, coagulation time by the Lee and White method, and prothrombin time were all normal. A small traumatic ulcer was found in the nose, submucous resection having been performed previously. However, this of itself was not considered sufficient cause for the severe epistaxis, especially in view of the abnormal condition of the blood.

Comment on Cases V and VI. Selected from a larger number of less definite cases of recurrent epistaxis, these show more clearly than the familial types the characteristics of mild hemorrhagic purpura.

Inquiry suggests that cases of mild recurrent epistaxis beginning in childhood and lasting for variable periods are quite common; the persons affected do not, as a rule, consult a physician. Many cases of this type are doubtless caused by local conditions in the nose, but it may safely be inferred that some of them are due to changes in the blood.

The characteristics of cases of familial epistaxis without telangiectasia, of those of recurrent epistaxis without telangiectasia but without familial history, and of the one family with recurrent adolescent epistaxis reported by Lane, indicate the probable existence of a familial form of purpura. A study of the abnormalities and familial characteristics of platelets which may be expected to elucidate the problem is under way. Some familial abnormality of the platelets would best explain the clinical facts.

LIVER DYSFUNCTION IN MIGRAIN.

With a Report of Thirty-five Cases.

By Joseph S. Diamond, M.D.,
NEW YORK CITY.

(From the Gastroenterologic Service of the Sydenham Hospital.)

Many views have been entertained as to the causation of migrain. The subject of hemicrania, sick or bilious headache, as it is commonly called, has always lent itself to many theoretical hypotheses, and few disorders have enjoyed such rich description from the pens of the medical masters who have themselves been subject to the disease.

During the age of the humoral theory, Galen believed that the black bile in the head was responsible for the migrain attack. In more modern times, the subject of migrain has occupied the domain of neurology, and diversified views as to its pathogenesis are still being contended. Moebius[1] attributed the attack to change in the cerebral cells. Spitzer[2] maintained that the temporary closure of the foramen of Monro, with the sudden distention of the ventricles was responsible for the attack. Likewise Auerbach[3] attributed the attack to an increase in intracranial pressure resulting from a disproportion between the size of the cranial cavity and its contents. Du Bois-Reymond[4] blamed the sympathetic and a labile vasomotor. Edinger[5] and Oppenheim[6] likewise attributed the attacks to vasomotor disturbances. The association of the attacks with the menstrual period led to the belief of an endocrine disturbance, especially the ovarian. Timme[7] attributes the dis-

turbance to the congenitally small sella which encases the pituitary body causing pressure and lack of proper development of the gland.

More recently, metabolic disturbances have received considerable attention. Retention of purin substances, intestinal toxemia, anaphylactic reactions, have all in turn been claimed as etiologic factors.

Yet in spite of the repleteness of literature and its versatility, no definite scientific data beyond empiricism and hypotheses have ever been collected to indicate a definite lesion or cause.

The common belief that the liver is responsible for this disorder has been handed down to us from the ancients, who believed that the vomiting of bile is an attempt of the system to rid itself of an excess of bile retained in the body.

With the introduction of liver-function tests into medicine, and their established utility, opportunity offered itself to test out a series of patients suffering with migrain, and thus ascertain whether the liver plays any part in this affection.

Thirty-five patients were so tested. The test included the van den Bergh estimation of bilirubin in the serum, and the urobilinogen test in the urine. The cases were carefully chosen and all those in whom other pathologic processes were found, were not included in this group.

Complete examinations were performed in every instance. The gall bladder was visualized by means of tetraiodophenolphthalein, and Roentgen ray series of the gastrointestinal tract were made in all patients who manifested the slightest gastric or abdominal symptoms also examination of the gastric contents, blood, urine, as well as blood-pressure estimations and eye examinations, were carried out in order to rule out symptomatic migrain. In several instances, gall-stone shadows were discovered; and though the migrain attacks were characteristic, these cases were not included in the group. In other instances, hypermetropic astigmatism was found, the headaches being promptly relieved by the correction of the error of refraction. None of these cases, however, are included in this series.

The results of the tests were quite striking. In 32 out of the entire series of 35 cases, there was evidence of disturbed liver function, as estimated by the van den Bergh reaction.[8] In 91 per cent of the series there was a bilirubin retention which varied from 1 to 5 units, the normal being 0.4 to 0.8 unit; 0.8 being equivalent to 1/250,000 bilirubin which is regarded as the upper normal level. In other words, all of these cases presented the so-called latent icteric stage; that is, where the concentration of bilirubin in the serum does not exceed the normal kidney threshold for bilirubin, which is from 4 to 5 units or 1/40,000. Above this level bile escapes into the urine.

The urobilinogen in the urine was variable. Figures rising at times as high as 1 to 200 dilution were found in the cases with higher

bilirubin retention. In the milder cases the urobilinogen varied from normal to slightly above normal, 1 to 35, the normal figures being about 1 to 20 dilution, as described by Wallace and the writer.[9] The urobilinogen in the urine is highest in the afternoon, and estimations should be made on a fresh specimen several hours after the midday meal, and not after purgation.

The high van den Bergh readings were a constant finding. They were present as well during the intervals between the attacks with but slight variation, indicating a permanent liver change.

Incidence. There were 21 females and 14 males. The preponderance of females corresponding to the statistics of Liveing[10] and those recently reported by Bramwell.[11] The ages varied from nineteen to forty-six years, the majority being below forty years. In over two-thirds of the cases, there was a history of onset in the first and second decade; the others dated the onset to the third decade. With few exceptions, most all gave a familial history, the transmission being, in the main, through the mother, although in several instances the father was a chronic sufferer with headaches. When the parental history was wanting, I could elicit the presence of the ailment in a sister or aunt. The frequency of attacks varied anywhere from four to six weeks in the milder cases to once or twice a week in the severe types.

Classification. Headache of the hemicranial type was present in all. Twelve cases were of the pure cephalic type without digestion upset. The characteristic periodic headache was the only outstanding symptom. In 15 cases, the headache was associated with nausea, vomiting, manifesting the so-called bilious attacks. In 8 cases, the gastric and abdominal symptoms predominated. There was definite abdominal pain simulating gall-bladder colic or gastric crises, which required morphin for relief. So manifest were the gall-bladder symptoms, that 3 of the patients were subjected to laparotomy and in 2 instances the gall bladder was removed in spite of negative gross findings. The periodic attacks of abdominal pain and vomiting, however, continued unabated after the operation. These are the types of cases that are spoken of as abdominal or visceral migrain.

The van den Bergh and urobilinogen reactions were lowest in the group with simple hemicrania (Table I) but higher in those associated with digestive upset (Table II), and were highest in the type classed as abdominal migrain (Table III).

In analyzing the last group, one finds a close analogy to the ordinary types of hemicrania. There occur the same hereditary factors, the periodicity, the persistance of the attacks for many years, with their inception in early childhood. The picture is identical, differing only in the preponderance of the abdominal symptoms. The attack always commences with the characteristic headache accompanied similarly by dullness of mentality, somno-

lence, photophobia, irritability to sound, ophthalmic pain, and so forth, gradually leading to pain in the upper abdomen, to nausea, and to intense vomiting of bile. I have never failed to elicit in these cases, the onset of the attack with headaches and nausea which distinguishes this type from the true gall-bladder colic in whom the headache, if at all present, is a later development.

TABLE I.—CASES IN WHICH HEADACHE WAS THE CHIEF SYMPTOM PRESENT.

Sex.	Age.	Van den Bergh (units of bilirubin).	Urobilinogen (dilution in urine).
Male	33	2.10	1:75
Male	33	1.75	1:50
Female	29	1.60	1:30
Female	37	1.50	1:35
Female	35	1.50	1:25
Female	46	1.45	1:25
Male	24	1.25	1:30
Female	29	1.20	1:35
Female	34	1.00	1:40
Male	30	0.80	1:20
Female	25	0.75	1:25
Female	23	0.75	1:30

TABLE II.—CASES IN WHICH HEADACHE WAS ASSOCIATED WITH NAUSEA AND VOMITING.

Sex.	Age.	Van den Bergh (units of bilirubin).	Urobilogen (dilution in urine).
Male	31	2.75	1:150
Male	28	2.25	1:100
Female	29	2.00	1:75
Male	25	2.00	1:50
Female	38	1.75	1:35
Female	36	1.50	1:40
Female	19	1.40	1:50
Female	28	1.35	1:40
Female	34	1.25	1:20
Female	33	1.20	1:25
Male	27	1.15	1.20
Female	40	1.10	1:30
Female	39	1.00	1:25
Female	33	1.00	1:20
Female	32	1.00	1:20

TABLE III.—CASES OF ABDOMINAL MIGRAIN WHERE HEADACHE AND GASTRIC UPSET WERE ASSOCIATED WITH SEVERE ABDOMINAL PAIN.

Sex.	Age.	Van den Bergh (units of bilirubin).	Urobilinogen (dilution in urine).
Male	29	5.00	1:200
Female	30	4.50	1:200
Female	33	3.75	1:150
Male	42	3.50	1:75
Male	39	3.25	1:100
Male	40	2.75	1:100
Male	28	2.25	1:80
Male	30	2.00	1:50

These cases must also be sharply differentiated from those in whom there is a continuation of biliary attacks after the removal of a definitely diseased gall bladder, for in this latter group, the pain is due to the presence of a similar infectious process in the larger ducts and often in the smaller biliary radicles, a choledochitis or cholangitis.

The following case illustrates a good example of what may be termed abdominal migrain:

CASE I.—Female, single, aged thirty-three years. Began in childhood with headache and vomiting spells occurring several times during the year. These were regarded as stomach upsets due to indiscretion. As she grew older, the attacks became more frequent and more pronounced. At the age of twenty years, she developed attacks of abdominal pain along with her headaches and one year later a diagnosis of acute appendicitis was made during one of these attacks, and the appendix removed. There was no change following the operation, the attacks persisting with the same periodicity, increasing in severity as time went on. The question of diagnosis revolved then about the gall bladder, and at the age of twenty-five years during an attack of abdominal colic, the diagnosis of acute cholecystitis was made and the gall bladder removed. The gall bladder was found to be normal, containing neither stones nor other evidence of pathology. While still in the hospital convalescing the patient developed a similar attack of headache, nausea abdominal pain, and vomiting. The operation had no influence whatever on her condition and during the eight years following the operation, she has become more incapacitated, the attacks recurring with greater frequency, at times as often as once a week. The patient came under my observation in October 1926, presenting a pale and sallow complexion with a definite icteric tint in the sclera. Examination revealed some tenderness along the lower border of the liver, no splenic enlargement; hemoglobin of 68 per cent; red blood cell count 3,900,000; white blood cell count 6500, and polymorphonuclears 65 per cent. The urine contained large amounts of urobilinogen, 1 to 150 dilution, no bile or albumin, and her van den Bergh reaction showed 3.75 units. She gave a lifelong history of constipation and the Roentgen ray series revealed a marked spasticity of the colon, retaining the barium scybalæ for five days. The patient said that the attacks always commenced with a sick headache over her left temple, shooting into the eyeball, face, occiput, and down to the neck. Soon she was seized with epigastric pain and vomiting, bringing up a good deal of bile. The pain radiated to the right and frequently to the back, being controlled, on many occasions, only by morphin. After enemata and drastic purgation, the attack came to a standstill, the patient remaining incapacitated for several days. She stated that in her earlier days, the eating of red meats would invariably bring on an attack the following morning, but of

late even white meats would do it, and fish, especially baked salmon, which never failed to induce an attack.

Constipation of the spastic type was a constant findings. This was noted from the small narrow scybalæ of the stool, as well as from the Roentgen ray examination where the transverse and distal colon appeared tightly constricted in the shape of a narrow ribbon. Many patients stated that an attack would invariably develop following the ingestion of red meats, canned and pickled meat or fish. Some were also susceptible to goose, duck, and turkey, and fresh salmon. So certain were they to come on that the more observant patients anticipated an attack after such indiscretions. If prompt catharsis was induced, the attack would be shortened, lasting a day. If, however, drastic purgation was delayed, the attack was prolonged to two or three days.

Other contributary factors which helped to precipitate an attack were fatigue, strain, emotional factors, worry, excitement, rage, sexual excesses, coitus interruptus, all of which tend to lower the general body resistance.

The blood pressure was found to be low in all patients of this series, averaging from 90 to 110 systolic, and 60 to 80 diastolic.

Discussion. The development of an attack following the ingestion of animal protein, especially during the period of constipation, brings up the question of intestinal toxemia and the relation it bears to impaired liver function.

Of late, the French have correlated certain anaphylactic reactions with the failure of the liver to synthesize into coagulable proteins, the amino bodies brought to the liver from the intestinal canal.

The syndrome, hemoclastic crisis, occurs when the liver is disabled, and is employed by Widal as a liver-function test. It is an allergic manifestation and consists of a fall in blood pressure and of a digestive leukopenia instead of the normal digestive leukocytosis. It is brought about by the ingestion of protein food in individuals with hepatic disease. Lubbers[12] of Holland also speaks of an "insuffisance proteopexique" responsible for the hemoclastic crisis.

The understanding of migrain becomes much simplified when we consider that toxic putrefactive substances reach the general circulation through the failure of the liver to synthesize and detoxicate them. A series of symptoms then arise which are the result of vascular changes in the cerebrum or other viscera which may be regarded anaphylactic in character and are analogous to Quincke's edema. Substances such as histamin and tyramin, putrefactive products derived respectively from the amino acids histidin and tyrosin, are extremely toxic and are known to produce vascular changes, the former vasodilatation, the latter vasoconstriction. A histamin effect could induce a vasodilatation of the meningeal or splanchnic vessels, causing an exudate and consequent edema of the nerve bundles, resulting in the characteristic symptoms.

Strümpel[13] was the first to regard migrain as an allergic manifestation and spoke of it as an exudative process, comparing it with urticaria and angioneurotic edema. Widal and Pagniez[14] in France, as well as Miller and Raulston[15] in this country, treated migrain on the basis of an allergic reaction using peptones for desensitization. Three patients of the series here reported developed intense urticarial eruptions, requiring adrenalin for relief.

The writer has no experience with skin tests in migrain. Vaughan[16] and Coke[17] cite several instances in which migrain reactions were obtained in wheat, sweet potatoes, beans, and cocoa. It would be of extreme interest to study the liver function in this group of cases.

Treatment. Marked beneficial results were obtained by changing the intestinal flora to Bacillus acidophilus and avoiding intestinal putrefaction. This was accomplished by withdrawing all forms of animal protein from the dietary, by placing the patient on a strict lactovegetarian diet, and by the use of lactodextrin and various forms of sour or acidophilus milk; also by overcoming the spastic constipation and producing copious daily evacuations. The liver is thus spared from being taxed with the toxic products of decomposition. The occasional use of cholagogues such as bile salts aid along in stimulating liver function. It is very essential in prescribing vegetarian diets, that the patients familiarize themselves in the culinary art of preparing vegetables in a palatable form so that the diet may be continued for longer periods. Needless to say, such patients require an equable life, avoiding undue physical and mental strain and emotional upsets. By following this régime, there was a marked amelioration in the general condition. Many patients became symptom free, while in those in whom the constipation was not so readily combated, the headaches when occurring, were very mild and evanescent.

The patient whose history is here reported has enjoyed comparative comfort for the first time in many years. She has had no abdominal pain in eight months, and only on two occasions when constipated has she had slight headaches, more in the nature of a dullness in the head, which was of short duration.

Summary. 1. Thirty-five cases of cephalic and abdominal migrain are here reported in whom liver-function tests were carried out. The tests comprised the van den Bergh reaction of bilirubin in the serum and the urobilinogen in the urine. The results indicate a definite liver disturbance. In 91 per cent of the cases, there was a state of latent icterus with a bilirubin retention of 1 to 5 units. The urobilinogen was also found to be increased from 1 to 35 up to 1 to 200 giving the highest figures in cases with high bilirubin retention. These may be classed as hepatic migrain.

2. The inability of the liver to detoxicate putrefactive substances, derived from animal proteins in the intestinal canal, is here discussed

and an attempt is made to explain the resulting symptoms as an allergic reaction.

3. Also mention is made of the beneficial results in the treatment by abstinence from animal proteins, changing the intestinal flora, and relief from the spastic constipation.

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REVIEWS.

MALARIAL PSYCHOSES AND NEUROSES. By WILLIAM K. ANDERSON, M.D., F.R.F.P.S. (GLAS.), Visiting Physician to the Eastern District Hospital, Duke Street, Glasgow; Recognized Teacher of Clinical Medicine, Glasgow University. Pp. 395, 22 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $13.00.

THIS is the first comprehensive work dealing with the nervous manifestations of malaria that has appeared in the otherwise voluminous literature on this disease. Following introductory chapters on the parasite, malaria in history, its effect upon character and race degeneration, the author takes up the pathology of the disease in particular the changes in the central nervous system. This portion of the work is beautifully illustrated with numerous colored plates. Then follow descriptions of the various forms of the nervous manifestations of the disease. Over 200 detailed case records are presented. There are also interesting chapters on malaria and alcohol, the medical legal aspects of malaria, and surgery in malaria. There are thirty-four pages of references that fully cover the subject; those interested in medical history will be particularly gratified by the numerous references to the writings of the ancients. The make-up of the book as a whole is excellent and the publishers are indeed to be congratulated. R. K.

THE CARE OF THE PATIENT. By FRANCIS WELD PEABODY, M.D., Professor of Medicine, Harvard Medical School. Pp. 48. Cambridge: Harvard University Press, 1927. Price, $1.00.

THIS little book should be read by every hospital intern and every senior medical student, for in very few pages, Dr. Peabody has encompassed a lesson that interns and students rarely learn until later years: the importance of the personal element in the practice of medicine. Dr. Peabody points out that particularly in hospital practice is the personal element apt to be lost sight of, and yet at all times "the secret of the care of the patient is in caring for the patient." R. K.

[Dr. Peabody's recent death—an incalculable loss to the medical profession—makes this probably the last work from his pen.—EDS.]

A Handbook of Diseases of the Stomach. By Stanley Wyard, M.D., B.S., M.R.C.P., Physician to the Bolingbroke Hospital and the Victoria Hospital for Children. Pp. 387; 32 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $5.00.

An interesting, sound and conservative presentation of the subject, a field in which only too often fads, eccentricities and, at times, near-charlatanism are rampant. The mode of presentation is original in the manner of arrangement. The interpretation of results of diagnostic methods and treatment indications are particularly well handled, and if one does not always agree with the writer's conclusions, one still feels that he has presented enough of both sides of the question to allow the reader his own choice. R. K.

Evolution of Preventive Medicine. By Sir Arthur Newholme, K.C.B., M.D., F.R.C.P., Formerly Principal Medical Officer, Local Government Board of England; Lecturer on Public Health Administration, School of Hygiene and Public Health, The Johns Hospkins University. Pp. 226; 6 illustrations. Baltimore: The Williams & Wilkins Company, 1927. Price, $3.00.

An outline of the history of Preventive Medicine, in its earlier chapters it is practically the history of medicine viewed from the standpoint of hygiene and public health. Then with the broadening of the field, the development of the more specific domain of preventive medicine is traced down to the present, omitting, however, because of limited space, some of the recent work in Tropical Preventive Medicine. The material has been wisely selected and is presented in a most interesting manner. The book is highly to be recommended to medical students in general as well as to those more interested in the special field of public health. R. K.

Overcoming Tuberculosis. By Gerald B. Webb, M.D. and Charles Ryder, M.D., both of Colorado School of Tuberculosis. Third edition. Pp. 80; 108 chart sheets. New York: Paul B. Hoeber, Inc., 1927. Price, $2.00.

This volume tells the story of sanatorium and health-resort treatment of pulmonary tuberculosis. The authors have well emphasized the importance of rest in bed during active stages of the disease, and they have placed proper stress upon diet and the

time necessary to bring about arrestment of disease. The chart sheets are each large enough to record temperature and pulse for a week, while there is space for general notes and questions to ask the physician.

Quotations from physicians and scholars are found on chart-sheets and these not only give hope to the patient but emphasize the importance of rest, feeding, fresh air and time in treatment of the disease. While intended for patients, general practitioners would do well to study these pages. I. K.

DENTAL EDUCATION IN THE UNITED STATES AND CANADA. Bulletin No. 19 of the Carnegie Foundation for the Advancement of Teaching. By WILLIAM J. GIES. Pp. 692. New York: The Carnegie Foundation, 1926.

AN intensive investigation into the present state of dental education in North America, with proposals for the future. From the beginning, in this country dentistry has developed as a profession separate from medicine, consequently under present conditions it cannot be made an integral part of medicine such as laryngology or gynecology. Nevertheless, importance of the mouth and teeth in relation to the body as a whole render necessary the recognition of dentistry as a part of health service of equal importance with other specialties of medicine. The plan proposed by the Carnegie Foundation for bringing about this result is now undergoing trial. Much that is stated in this book should concern deeply those interested in medical education, since the latter also at the present time is thought by many to be due for radical changes. R. I.

MODERN CLINICAL SYPHILOLOGY. By JOHN H. STOKES, M.D., Professor of Dermatology and Syphilology in the School of Medicine, University of Pennsylvania, Formerly Head of the Section on Dermatology and Syphilology, The Mayo Clinic, Rochester, Minnesota. Pp. 1144; 865 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $12.00.

A TRULY remarkable book that will take its place among the classics of medicine.

It may be subdivided into two parts. The first half deals with the general principles of pathology, diagnosis and treatment of syphilis. The latter half goes into the details of differential diagnosis, special pathology of the various system involvements and the like.

The opening chapter states the present problems and knowledge of the disease: a cannily placed discussion to wean away the reader from the preconceived notions left us by earlier clinical syphilography. Then follows a chapter on the clinical approach to syphilis, in which it is pointed out that the greatest obstacle to recognition of the disease is a low index of suspicion among medical men. Next come chapters on physical examination for syphilis; the fundamental diagnostic tests; the fundamental principles of treatment; mercury, bismuth, iodides and the arsphenamines: their pharmacology, toxicology and mode of administration; operating room and treatment technique; clinical reactions, complications of, and contraindications to, treatment; collateral factors in treatment: rest, and so forth; the problems of latency, arrested disease, hygiene and prophylaxis.

The latter half of the book presents chapters on the diagnosis of early syphilis (chancre, secondary skin lesions) with many excellent illustrations to make clear the differential diagnosis from other skin conditions; the treatment of early syphilis; the landmarks of late syphilis on skin and mucous membranes; late syphilis of the skeleton (points well made by a "dry clinic" of many illustrative cases); syphilis of the gastrointestinal tract, liver and spleen, of the cardiovascular system, late syphilis of the nervous system; familial and prenatal syphilis, miscellaneous aspects and case memoranda (syphilis of lungs, mediastinum, kidney, genitalia, and so forth; public health problems.

The book is obviously the work of a teacher. Presented in the first person, the style is always vivid and forceful. Many teaching devices (illustrative cases, material in tables, heavy type for special emphasis, numerous well-chosen illustrations) are used throughout. By using small type for the discussion of rarer conditions, an unusual amount of material has been brought within the limits of a single volume.

There is very little to criticize in the work. The author is an enthusiast but manages remarkably well to keep both feet on the ground. It is a pity, perhaps, that so authoritative a work should not sanction and further the more proper biologic term "treponema pallidum" instead of the older "spirocheta pallida" (yet all the illustrations of the organism are labelled "treponema pallidum"!). In the chapter on syphilis of the liver and spleen, the author is possibly a bit unappreciative of the clinical diagnostic difficulties. While a full bibliography would have been unwieldy, some footnote references to original sources would be welcome.

However, these are all minor points, and quite fade out before the many excellences of the work. Adapted not only to the needs of the student, but also meeting the requirements of many special fields of medicine, the book should have a universal appeal.

R. K.

BOOKS RECEIVED.

Surgical Anatomy. Volumes II and III. By JOHN B. DEAVER, M.D., Sc.D., LL.D., F.A.C.S. Second edition. Pp. 854 and 763, 195 and 160 illustrations. Philadelphia: P. Blakiston's Son & Co., 1927. (To be reviewed later.)

American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, M.D., Fourteenth edition. Pp. 1388, 319 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $7.00 plain; $7.50 thumb index. (To be reviewed later.)

Collected Papers of the Mayo Clinic and The Mayo Foundation, 1926. Pp. 1329, 386 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $13.00.

Medical Clinics of North America. Chicago Number, July 1927. Pp. 294, 26 illustrations. Philadelphia: W. B. Saunders Company, 1927.

Medical Clinics of North America. St. Louis Number, September, 1927. Pp. 322, 48 illustrations. Philadelphia: W. B. Saunders Company, 1927.

The Anatomy of the Nervous System. By STEPHEN RANSON, M.D., PH.D. Third edition. Pp. 425, 284 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $6.50. (To be reviewed later.)

Diagnosis and Treatment of Diseases of the Stomach. By MARTIN E. REHFUSS, M.D. Pp. 1236, 519 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $12.00. (To be reviewed later.)

A Text-book of Pathology. By ALFRED STENGEL, M.D., Sc.D. and HERBERT FOX, M.D. Eighth edition. Pp. 1138, 570 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $10.00. (To be reviewed later.)

Surgical Clinics of North America. Chicago Number, June, 1927. Pp. 330, 81 illustrations. Philadelphia: W. B. Saunders Company, 1927.

Hämatologisches Praktikum. By HANS ZIEMANN. Pp. 166, 37 illustrations. Berlin: S. Karger, 1927. Price, gold marks, 7.20.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Twenty-six Thousand Kahn Tests Compared with the Wassermann Test.—The proof of the value of the Kahn test for syphilis is gradually piling up in reports of thousands of comparative examinations by this method and the Wassermann reaction in which the former is found to be as accurate as the latter. Two additional publications would seem to substantiate further the already adduced evidence of the Kahn test's value. The first, HULL (*J. Am. Med. Assn.*, 1927, **88**, 1865), points out some of the advantages of the precipitation test over the complement-fixation reaction. They include: Savings of time in carrying out the technique, a few minutes with the one and eighteen hours with the other; a saving of labor, the one doing away with the constant daily attention to the sheep cells, complement and amboceptor; saving of cost, obviating the up-keep of several sheep, many guinea pigs and rabbits; the ability of carrying out the test with anticomplementary specimens, or hemolyzed and old specimens; lastly, the advantage of simplicity, with less possibility of technical error. All these advantages would be of no amount if the Kahn test was not as accurate as the Wassermann. Reliability and trustworthiness of a test are a requisite of such an important examination as that of the blood or body fluids to determine the presence or absence of syphilis. In the 26,000 specimens examined by the author he has found that there was relative agreement in 97.8 per cent between the two tests. In the 200 cases which disagreed the clinical histories indicated that the Kahn test is more sensitive than the Wassermann. The second publication, **Report on Three Hundred Thousand Kahn Tests,** by KAHN, KENDRICK and LANDAU (*J. Am. Med. Assn.*, 1927, **89**, 84) is presented by

the original describer of the precipitation reaction for syphilis with collaborators. Comparable Wassermann and Kahn tests were carried out in 174,580 serums. In the earlier procedure there was an absolute agreement of 94.17 per cent between the two tests. With the present technique there is an absolute agreement of 96.77 per cent and no agreement in 0.61 per cent. It is of interest to note that in 8661 treated cases the results were identical in 5727 examinations, the Wassermann results were stronger in 594 and the Kahn in 2340. In the latter part of 1925 the Michigan Department of Health abandoned the Wassermann reaction. Since then 125,000 Kahn tests were reported to the Michigan physicians, with considerable satisfaction to them owing to the greater rapidity with which the report could be received, particularly in an emergency, such as blood transfusion when a report could be made in one hour. The present report by the originator of the test is not a hyperbolic, distorted presentation by an enthusiast carried away by his thesis but a definite, didactic statement with supporting figures and other confirmatory data.

The Experimental Production of Immunity Against Metazoan Parasites and an Investigation of its Nature.—BLACKLOCK and GORDON (*Ann. Trop. Med. and Parasitol.*, 1927, **21**, 181) present in a long communication the proofs of their experimental studies that immunity against metazoan parasites may be acquired by a test animal. It has long been known that man and animals develop an immunity against such parasites as they increase in age. An old dog, for example, will harbor few if any ascaris whereas in pups these worms are extremely common. A similar difference is found in man in adult life and childhood. The authors in their work do not consider age immunity, but employ the following rigid definition: "An immunity acquired as the result of previous infection or vaccination and involving the death of the metazoan parasite in the host within a specified time." The technique employed briefly consisted of the application of the larva of Cordylobia anthropophaga to certain areas, back, scrotum, abdomen and skin of the feet. The penetration and development of the larvæ into the skin was considered evidence of lack of immunity, the death of the larvæ as proof of an immunity. It was found that larvæ applied for the first time survived in percentages of well over 50. A second application showed that by the sixth, or standard, day for examination nearly all of the larvæ had died while in repeated applications there survived none of the larvæ. This immunity was found to be primarily a local immunity but proofs were adduced from later experiments which showed that immunity does not remain localized. On the contrary, it spreads outward in a gradually weakening zone from the areas originally immunized. It was found that this immunity persisted for at least three months, probably much longer. The nature of the immunity was then studied. That there is but little association of the immunity and the general circulation is shown by: (1) Failure to confer passive immunity from an immune to a nonimmune guinea pig; (2) failure to produce immunity by intraperitoneal or subcutaneous injections of first or third instar larvæ; (3) absence of parasiticidal properties from the blood of immune animals; (4) failure to secure positive precipitin and complement-fixation reactions. That the

immunity is directly associated with the tissues is shown by the fact that the skin of an immune animal can destroy larvæ, that immunity persists in skin grafted on nonimmune and skin reactions are present in immune and semi-immune areas in animals previously infected. The immunity is not dependent upon damage to the skin nor upon athrepsis and it is a "solid" immunity. Anaphylaxis may be discounted as it was never produced. From this study, briefly outlined, evidence if brought forth which shows that while a metazoan immunity exists it is "governed by laws which differ widely from those governing bacterial immunity."

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Sarcoma of the Rectum.—WEEKS (*Surg., Gynec. and Obst.*, 1927, **44**, 478) says that rectal sarcoma is a very rare lesion. Approximately 100 cases are to be found in the literature. If doubtful cases were excluded the number would be reduced to one-half. The reported case is of a large spindle-cell sarcoma in a man aged forty years, who died of generalized sarcomatosis seven months after the appearance of the first symptom. The symptomatology of the ulcerative sarcomata differs but little from that of carcinoma. Carcinoma ulcerates more quickly, starts cachexia sooner, involves the lymphatics while sarcoma involves the blood stream. Carcinoma practically is never pigmented and generally gives rise to more pain than sarcoma. Roentgen ray and radium are valueless in the treatment. An early and very radical operation is indicated, because of the rapid and fatal metastasis which take place through the blood stream.

Papillomatous Tumors of the Breast.—HART (*Arch. Surg.*, 1927, **14**, 793) claims that the benign papillomatous cyst is a distinct type of tumor, presenting a fairly uniform history and physical findings. A nipple discharge, usually bloody, occurred in 66 per cent of these cases. This tumor gives a nipple discharge without a palpable nodule. The benign tumors have appeared at any age after puberty. The malignant appeared only after thirty-five years of age. Upon pathologic examination the cysts show one or more papillomas, a thin wall and no invasion. Frequently there are multiple cysts, and about these all types of epithelial proliferation, duct adenoma, cystic adenoma and nonencapsulated adenomatous areas with associated hemorrhage into the tissues or a superimposed infection, these giving a fibrous prolifera-

tion. A large percentage of the cases in the malignant group gave the picture of cancer clinically, grossly and microscopically. The cancer may apparently arise from the papillomatous cyst or occur in a breast the seat of one or more of these tumors. The duration usually is short, but in 1 case the tumor was present for thirteen years, suggesting a benign growth for eleven years with malignant change about the time of or following incision. No other patient gave a history that would suggest malignant change in a benign tumor.

Unexpected Deaths in the Postoperative Period.—SHORT and FRASER (*Brit. Med. J.*, 1927, **215**, 1001) report that there were 7 deaths on the table in 16,000 operations. Two were anesthetic deaths; 4 must be attributed to the surgical procedure, while the remaining case was moribund from strangulated umbilical hernia and died after inhaling only a few drops of ether. In pulmonary complications it is not probable that sepsis *per se* gives rise to the bulk of the lung complications. Pneumonias rarely followed operations for cellulitis, pyemia and abscesses. The operative procedure on the upper abdomen probably gives rise to reflex inhibition of the diaphragm, which in its turn is followed by collapse of the lung and that again by infection. On our present information the following rules should be observed: to avoid as far as possible operating on patients with bronchitis or to operate under local anesthesia. There should be careful guarding against inhalation of vomit. There should be as little moving through cold corridors as possible on the way back to bed. The use of novocain or quinine-urea reduces the inhibition reflex in upper abdominal operations. No drainage tubes should be placed just under the liver to impede its descent. Contrary to the usual opinion pulmonary embolism seems to be a rare cause of sudden postoperative death in the study of this large series of cases. What had been diagnosed as pulmonary embolism generally turned out to be a sudden cardiac failure. To avoid postoperative hemorrhage, it is wise to use a three-cast knot instead of two and to transfix with a needle if the hold will not be perfectly reliable. If the patient is jaundiced, coagulation time should be noted. If delayed, prophylactic intravenous injection of calcium chlorid should be given. It was noted that most deaths from shock were after gall-bladder surgery. It is probable that there was some underlying defect in the liver. We now know that the patient may look and feel in good health and yet the kidneys may be on the verge of a final breakdown. The routine kidney studies and the two-stage operations in renal disorders have reduced the mortality, but it seems that further improvement can be obtained.

The Character and Treatment of Bladder Ulcers.—KEYES (*Cornell Univ. Med. Bull.*, 1927, **16**, 167) believes that chronic inflammatory ulcerations of the bladder may be grouped into three classes, viz.: tuberculous ulcers, ulcers of the so-called Hunner or elusive type and incrusted ulcers. The incrusted ulcer is a thing apart apparently due to a special type of coccic infection often located on the trigone and about the bladder neck, often clinically and cystoscopically simulating carcinoma, yet often readily curable by local applications of argyrol or acidophilus or Bulgarian bacillus. The elusive ulcer, occurring in the mobile part of the bladder away from the trigone and urethra, is sometimes asso-

ciated with tuberculosis, sometimes with generalized cystitis and pyelitis. Indeed it is not yet proven that the submucous lesion is not rather the remnant of an acute generalized cystitis than a specific entity. Hence the great variety of treatments that succeed in individual cases. Operation has a place as the last resort to get rid of ulcers so chronically infiltrated that no other treatment will heal them. Tuberculous bladder irritability persisting for years after nephrectomy may be due to a variety of causes, among which tuberculosis of the remaining kidney and of the urethra (causing partial retention of urine) are prominent. Moreover, the bladder lesion of chronic tuberculous cystitis may be a pure tuberculosis, but is more often a mixed infection. Discreet treatment of the bladder may, even in the presence of the tuberculosis of the prostate or of the remaining kidney marvellously relieve the symptoms. It would seem, however, that in certain bladders the mixed infection supersedes the tuberculosis in part or even wholly and the lesions conform to the type of elusive ulcer.

Prevention of Regeneration of the Ribs.—HEAD (*Arch. Surg.*, 1927, **14**, 1209) state that in many thoracic operations regeneration of the resected ribs prejudices the result. Heretofore regeneration has been prevented by removing the periosteum with the ribs. This increases the risk of perforating the pleura and producing a pneumothorax or pyothorax. The bone-forming elements left after subperitosteal resection can be destroyed by chemical cauterization. Cauterization with silver nitrate stick consistently and with 50 per cent silver nitrate solution occasionally produced a deep necrosis and perforation into the pleural cavity. Cauterization with concentrated solution of chromic acid and with Zenker's solution prevented regeneration of bone and did not perforate the pleura. The results with Zenker's solution were the more satisfactory.

Intrascrotal Lipomata—CECIL (*J. Urol.*, 1927, **17**, 557) says that it is rare to find a solid mass of fat occurring within the scrotum. Such cases may simulate tumors of the testicle. The tumor, however, lies upon the testicle, but outside the tunica vaginalis. Apparently it has originated in or immediately adjacent to the spermatic cord and has separated in its growth the different structures of the cord. The testicle is somewhat smaller than normal, but otherwise appears to be of normal structure. No fat was found in the testicle itself. Examination of the specimen reported leads to the conclusion that its blood supply is so intimately associated with the fatty mass that the mass could not have been removed and the blood supply of the testicle maintained.

Relation of the Reticuloendothelial System to the Splenomegalies Associated with Nonspecific or Secondary Anemia.—WHIPPLE (*New Orleans Med. and Surg. J.*, 1927, **79**, 800) claims that in a certain group of splenomegalies that respond to surgical therapy there is an associated anemia secondary in type and showing no specific blood picture. The deranged functions of the spleen in these clinical entities would seem to be due to the derangement of the reticuloendothelial apparatus. The extent to which the derangement of the reticuloendothelial cells is limited to the spleen determines apparently the efficiency of splenec-

tomy. The capacity of the reticuloendothelial cells of parts of the reticuloendothelial apparatus outside the spleen to take over physiologic and pathologic activities of the spleen compromises the prolonged period of relief following splenectomy in such conditions as thrombocytopenic purpura hemorrhagica. These reticuloendothelial cells are the great phagocytes of the body called clasmatocytes by Ranvier and macrophages by Metchnikoff. They engulf cells, cell products and cell detritus and parasites of all kinds from bacteria to minute inert foreign bodies. The site of greatest phagocytic activity varies in different species; in birds for instance it is most active in the liver, in omnivorous mammals this is most pronounced in the spleen.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D., OF PHILADELPHIA.

A Study of Two Hundred and Two Cases of Congenital Syphilis.—CANNON (*J. Am. Med. Assn.*, 1927, **89**, 666) studied 202 cases of 181 mothers, and he found that the more recent the infection in the mother the more frequently the children were affected and the severer the type of infection. Only 23 per cent of the mothers had received treatment before or during pregnancy. The greater number of these cases represented the first pregnancy. The average age at which symptoms developed was between the tenth and fifteenth years. Ninety-one per cent of the patients were normal mentally. Interstitial keratitis was the most frequent symptom occurring in 35 per cent of the cases. Dental defects were the most common physical sign. The Wassermann reaction and organic luetin tests were strongly to moderately positive in all but 2 cases. Spinal-fluid tests were positive in 10.5 per cent. The plan of treatment was continuous. There were 14 cases of syphilitic nephritis, all of which were fatal and all were studied at autopsy. The 4 cases of meningitis were all fatal and 3 of these were examined at autopsy. In this series in those cases in which treatment was begun early in infancy the Wassermann reaction became negative after about four courses of arsphenamin and mercury and remained so. A relapse to a positive Wassermann reaction after the serum had once become negative was rare.

Parenchymal Pulmonary Tuberculosis in Children.—GIBSON and CARROLL (*Am. Rev. Tubere.*, 1927, **15**, 665) found in 855 children under fifteen years of age more than 10 per cent showed definite tuberculous disease of the parenchymal lung tissue. A definite history of exposure to an open case of tuberculosis was obtained in less than half of the cases. Measles, pertussis, influenza, and tonsillitis were the most frequent diseases. Cough, loss of weight, fatigue, expectoration and fever were the most prominent symptoms. Night sweats occurred with less

frequency than in adults, but proved to be of grave prognostic omen. Hemoptysis occurred about as frequently as night sweats, but was not of grave import that it usually is in adults. An excellent general appearance and lack of symptoms did not preclude the possibility of widespread tuberculosis of the lungs. Forty-nine of the patients died; 17 are alive with the active disease, and 19 reached a stage of arrest and continue well at the time of the report. Of the total deaths 71 per cent were among the female patients and 29 among the male. The establishment of puberty in the females increased the gravity of the prognosis. Complications were few but of ill omen. The presence of tubercle bacilli in the sputum of children is an almost positive sign of an unfavorable ending.

Growth of the Thymus.—Boyd (*Am. J. Dis. Child.*, 1927, **33**, 867) states that the thymus in the new-born child shows a temporary loss of weight which probably is concomitant with the normal loss of weight. The fetal type of thymus is broad while the infantile type is elongated. This change in form is produced during the first two weeks of life by the expansion of the lungs. Thymic symptoms may be produced during the first year of life by mechanical pressure of a normal gland on mediastinal structures, especially on the recurrent laryngeal nerve. The author could not show from her records that pressure on the trachea caused death. The anatomic picture of status thymicolymphaticus represents the normal thymus and lymphoid tissue of the well-nourished child. Failure to recognize accidental involution has caused the confusion regarding thymus weight and the misconception of status thymicolymphaticus. The average weight of the thymus found at necropsy in well-nourished children is 13 gm. at birth, 20 gm. at six months and 35 gm. at thirteen years. The average weight of the thymus found at necropsy in poorly nourished children is 8 gm. at two weeks, 6 gm. at six months, and 13 gm. at thirteen years. In general, the fluctuations in the weight of the thymus at any age period are coincident with fluctuations in body weight. Some illnesses, such as influenza, may affect the thymus before they affect body nutrition. The growth curve of the thymus in a well-nourished child is the same type as that of lymphoid tissue in general.

Transfusion in Childhood.—Sidbury (*J. Am. Med. Assn.*, 1927, **89**, 855) reminds us that transfusion in childhood is a valuable therapeutic measure and he feels that it should be more generally used. Cross matching before each and every transfusion, with fresh specimens of blood is the only safe method of blood matching. Bloods should be cross matched regardless of the age of the patient. In patients who have been given transfusions with incompatible blood, exsanguination transfusion is indicated. Too little emphasis is put on hemolysis reaction in blood matching. The indications for transfusion are increased as more is learned of the beneficial effects of blood in disease. Severe toxemias, as seen in severe burns, erysipelas, acute intestinal intoxication, toxic pneumonia, septicemia, infectious diarrhea, and carbon monoxid poisoning are greatly benefited by exsanguination transfusion. Long drawn out respiratory infections are greatly benefited and their course shortened by the giving of one or more transfusions. Mal-

nourished patients with secondary anemia begin to gain weight without any alteration in diet after a transfusion.

The Law of Puberty.—LIPSCHUTZ (*Deutsch. med. Wchnschr.*, 1927, **53**, 1079) says that the time of the characteristic changes in the genital tract and breasts is determined by a change in internal conditions which act on the sex glands and not by a primary change in the glands. Implantation of an immature ovary in an immature animal is followed by late appearance of sexual desire. If such an ovary is implanted in an adult animal the action of the ovary is apparent in two weeks. He implanted one-half of an ovary from an adult guinea pig in a three-months old castrated male, and the other half in a two-weeks old castrated male. The typical hyperplasia of the mammary gland started in the adult castrate in two weeks and in the young one in six weeks. In an immature animal the ovary remains inactive until the conditions necessary for the ripening of its follicles are present. One of these conditions seems to be identical in both sexes and is probably due to the production of a hormone by the anterior lobe of the pituitary. The other conditions seem to be different for the two sexes. The ovary implanted in castrated males does not develop corpora lutea but remains in the active stage of secreting follicles. This may account for the fact that in these castrated males the mammary glands grow larger than in females and even produce milk. It does not produce milk in castrated females. Implantation of sex glands in patients with infantilism is usually useless since the condition which keeps the patient's own glands from functioning persists. After the intervention the patient harbors three inactive glands instead of two.

Lactic Acid Milk Mixtures.—MARRIOTT (*J. Am. Med. Assn.*, 1927, **89**, 862) describes the preparation of lactic acid milk. The syrup is mixed with some water, the lactic acid added and the whole made up to the final volume. The mixture should be kept in a cool place, but on account of its high acid content it keeps perfectly for several days. This is made of Karo corn syrup, 3 ounces; lactic acid, U. S. P., 1 teaspoonful and water to make 1 pint. In making up the feedings, equal parts of unsweetened evaporated milk and the acid sugar combination are mixed. This is done by pouring the acid solution into the milk, which is then mixed by shaking or stirring. An entire day's feeding may be prepared at one time. Such formulas are far safer than those prepared from a questionable milk supply. The usual dilution of evaporated milk is with equal parts of water. To the half diluted milk 10 per cent by volume of karo is added and then 10 drops of lactic acid for each ounce of evaporated milk used. From all the evidence available the fat-soluble vitamins A and D and the vitamin B are not injured by the processes employed in the preparation of the evaporated milk. The antiscorbutic vitamin C is destroyed and it is essential that the formulas be supplemented with orange juice or tomato juice daily. It is also advisable to administer during the winter months as much as 1 teaspoonful of codliver oil daily.

Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1927, **33**, 880) found among the diseases and conditions responsible for initiating the

onset of asthma pertussis, 15 per cent; acute pneumonia, 14 per cent; measles, 4 per cent; tonsillectomy and adenoidectomy, 3 per cent; scarlet fever, 2 per cent. This was a total incidence of 38 per cent. Measles, acute pneumonia and diphtheria had a temporarily beneficial action on the course of asthma. Pertussis aggravated asthma. The incidence of chronic bronchitis and emphysema with deformity of the chest was 12 per cent and without deformity of the chest was 8 per cent making a total incidence of 20 per cent. The frequency, intensity and the prolonged duration of attacks were the factors principally responsible for the production of the deformity of the chest. Hypertrophied and diseased tonsils and adenoids did not act as a causative factor of the asthma. In 3 per cent of the cases tonsillectomy and adenoidectomy aggravated the asthma. The removal of the tonsils and adenoids did not relieve the asthma except in one case in this series and in that one the relief was only temporary. Chronic unresolved pneumonia as an etiologic factor occurred in 2 per cent of the cases of the entire series. These patients dated their asthma from an antecedent pneumonia. They were protein nonsensitive and were not tuberculous. Subacute pulmonary infiltration occurred in 11 per cent. Physical overexertion, indiscretion in diet, especially the eating of ice cream and the drinking of iced liquids, variations of weather, the change of seasons and exposure to winds and freshly painted rooms were important contributory factors in inducing asthmatic attacks. Allergy of itself cannot be explained on a basis of protein sensitization, because the sensitizing substances in themselves are merely exciting factors and not the basic cause of symptoms.

GYNECOLOGY

UNDER THE CHARGE OF

AND

FRANK B. BLOCK, M.D.,
INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Nonspecific Protein Therapy in Gynecology.—Parenteral injections of nonspecific proteins have been used in the treatment of many inflammatory diseases on the theory that such injections will stimulate the resistance of the body. The gynecologists have not been slow to recognize the possibilities of such a treatment especially in dealing with pelvic inflammatory disease, although the results obtained seem to vary with the enthusiasm of the individual physician. As a result of his experience in a small group of cases, AVERETT (*Am. J. Obst. and Gynec.*, 1927, **13**. 238) concludes that nonspecific proteins have a definite and valuable place as therapeutic agents in the treatment of

gynecological infections. He believes that their judicious use will replace surgical intervention in some cases and will thereby not deprive women of the sex organs and will enable them to continue the menstrual and reproductive functions. He has found that following the use of these proteins there develops a leukopenia, with a decrease in the polymorphonuclear leukocytes and a relative lymphocytosis, which supports the theory that the beneficial effect of the treatment is due to an increased lymphogenesis and lymph flow to the region of the infection. A febrile reaction with its train of disagreeable symptoms is not considered essential in the successful use of this form of therapy. In using a fat-free milk of low bacterial count he has had good results without a reaction and with very little discomfort to the patient. The best results were obtained in the acute and subacute pelvic infections, before dense adhesions have had time to develop. The immediate effect of the injection is the disappearance of pain and the development of a sense of well-being. Without desiring to discourage this type of investigative work, it is my personal feeling that most of these acute infections are self-limited insofar as symptoms are concerned and we should not place too much emphasis on the value of this form of treatment.

Improved Technique for Hysterectomy.—There are few operations which have become so well standardized as supravaginal hysterectomy and the results of this operation have been so satisfactory that it would seem that there could not possibly be any room for improvement in the technique. In certain cases, however, when there is a foul discharge exuding from the cervical canal, it has often been considered that a complete hysterectomy should be performed in order to obviate the danger of contaminating the peritoneal cavity with the discharge when the uterus is cut across in the supravaginal operation. It is fairly well established that the mortality and morbidity of the complete operation is higher than that of the supravaginal amputation and in order to have the advantages of the lower mortality and time conservation of the latter operation together with freedom from danger of contamination from a foul discharge CULLEN (*Surg. Gynec. and Obst.*, 1927, **45**, 80) presents a point in the technique of the supravaginal operation which he has found quite useful in cases of this type. After tying off the ovarian and uterine vessels and isolating the cervix, he carries a stitch through the cervix from before backward on one side of the cervical canal. He then rethreads the loose end of the suture and carries it through the other side of the cervix. The two ends of the suture are then tied together on the posterior surface of the cervix and the uterus is then amputated below the suture. It will be seen that the introduction of this mattress suture effectually closes the uterine canal and prevents the leakage of any infectious meterial from the uterus when the cervix is cut across. This operation is not recommended for cases of carcinoma of the uterine body but for those cases in which there is a degenerating myoma and it seems to be a small point which is well worth remembering.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

The Two-stage Operation for Suppurative Frontal Sinusitis with External Manifestations.—Further experience with the surgical management of cases of suppurative frontal sinusitis with external manifestations has convinced LILLIE and ANDERSON (*Arch. Otolaryngol.*, 1927, **5**, 152) that the two-stage, intranasal and radical, operation is satisfactory. The first stage consists in enlarging the nasofrontal duct by removal of the agger nasi under local anesthesia. When drainage has been well established by this method the second, or external radical, stage can be avoided in certain instances in which it might have suggested itself primarily as the method of choice. If, however, the second-stage operation becomes necessary the authors employ the technique as outlined by Lynch, Killian, or Lathrop, believing that the type of operation should be adapted to the patient and not the patient to the operation. As a rule, the Beck incision, below the eyebrows, was used. Bevelling of the outer edges of the external table prevents the formation of pockets which might defeat the purpose of the operation and lessens the external deformity under certain conditions. Sixty cases, all presenting some external manifestations of the disease, are analyzed as to condition on admission, previous operations and pathologic changes found at operation. Of these, the two-stage operation was performed on 24 patients; in 19 it was necessary to do the primary or intranasal stage only; in 17 the external operation, without the previous intranasal maneuver, was done. The authors emphasize the advisability of eradicating coëxisting infections of the upper respiratory before the sinus operations are undertaken, in order to lessen the danger of acute postoperative infections and meningitis. If the operation has been complete no external drainage is needed and reoperation is not necessary.

A Harmless Mucous Membrane Irrigant.—During the last several years the nose and throat surgeons have given up increasingly the use of irrigating solutions in the treatment of acute or chronically inflamed accessory sinuses or after these have been operated on. The feeling seems to be general that their employment is harmful, and it is frequently maintained that they spread infection. The saturated boric acid solution or the so-called physiologic salt solutions commonly used in hospitals (solutions of sodium chloride, varying in concentration from 0.7 to 0.85 per cent) at times unquestionably produce such bad effects, and yet, it must appeal to every one's surgical sense that the mechanical cleansing of mucous membranes, coated with mucus or pus, can by itself be only of benefit. Convinced that the evil effects produced by such irrigants were dependent on faulty composition, FISCHER and BLEDSOE (*J. Am. Med. Assn.*, 1927, **88**, 1881) have devised a hypertonic solution consisting of sodium chloride, 10.5; cal-

cium chloride, 0.84; potassium chloride, 0.42; water sufficient to make 1000. The mixture contains the three salts originally employed by Ringer, but the higher concentrations diminishes the likelihood of edema which is alleged to increase the suceptibility of tissues to infection. As calcium chloride is deliquescent, powder mixture is not stable and the authors advise keeping a saturated stock solution in proportions given by them. This can be properly diluted for clinical use and sterilized without fear of deterioration. In practice the solution is agreeable and harmless, the authors maintain.

Effect of Antiseptics on Nasal Flora of Rabbits.—After a series of observations, BULL and BAILEY (*Am. J. Hyg.*, 1927, **7**, 185) found that bacteria could not be completely removed from the upper respiratory passages of rabbits by the topical application of various antiseptic substances. The nasal discharge attending snuffles was unaffected by the instillation into the nares of appropriate solutions of such drugs as zinc sulphate, mercurochrome, argyrol, phenol, dichloramine, crystal violet, brilliant green and acriflavine. Nor did these medicaments remove the pathogenic microörganisms from the nasal cavities. Bacillus bronchisepticus, however, could be eradicated from the nasal secretions by mercurochrome. Although a diminution in several of the lesser pathogenic bacteria occurred after the introduction of dichloramine, crystal violet and brilliant green, the more pathogenic bacteria often increased in incidence at the same time. No injury to the nasal mucosa was observed after the use of mercurochrome, zinc sulphate, colloidal silver and phenol in the strengths employed. On the other hand, acriflavine was found to be mildly irritative and dichloramine, crystal violet and brilliant green acted definitely as irritants. Moreover, pneumonia often followed the employment of crystal violet and brilliant green.

Chancre of the Nasal Septum.—ZEISLER (*J. Am. Med. Assn.*, 1927, **88**, 1702) calls attention to the possibility of intranasal primary syphilis, by reporting 3 cases occurring in men, aged thirty, forty and forty-five years, respectively. He says the most important point in the early diagnosis of a hard chancre of the nasal septum is the erosion or ulceration with indurated borders which bleed readily and do not perforate the septum. The discrete, painless submaxillary bubo is also of diagnostic aid, as is the dark-field examination of suspicious ulcers or erosions of the septum.

Osteoma of the Frontal, the Maxillary and the Sphenoid Sinuses, with Report of Cases.—In reporting 3 illustrative instances of osteoma of the frontal, the maxillary and the sphenoid sinuses, GARRETTSON (*Arch. Otolaryngol.*, 1927, **5**, 135), reviews the literature on osteoma of the paranasal sinuses. About 215 cases of either a single osteoma or multiple osteomata have been reported from all sources. The point of origin appears to be, as a rule, in the floor of the frontal sinus. These tumors, in general, occur in the young when the bones are undergoing the greatest developmental activity. They may be hard and eburnated, compact or spongy, and have been known to vary in size from that of a bean to that of a good-sized potato. Growth usually is slow. The tumors are more or less encapsulated, possessing a hard outer cortex

which surrounds a softer, cancellous center. The covering mucosa often shows polypoid degeneration. If the nasofrontal duct is obstructed a mucocele of the sinus results. The chief local symptom is pain at the site of the osteoma, although there may be no subjective symptoms. The symptoms due to pressure on adjacent cavities depend, of course, on the cavity involved and upon the extent of the encroachment. The older cases were reported principally as tumors of the orbit, in which proptosis, diplopia and optic nerve derangement were prominent features. In the intranasal type, external nasal deformities and nasal obstruction may be present. In those which involve the internal plates, meningitis may be the first symptom. The diagnosis can often be made only by Roentgen ray examination, especially in the eburnated forms. When possible, the treatment is complete surgical removal. Since the advent of aseptic surgery the prognosis has been better, as the postoperative mortality has been lessened.

Torus Palatinus.—Torus palatinus is the term used to designate a thick, broad, hard elevation on the roof of the mouth, mesially. According to Merkels, it results from an unusual prominence of the bony borders of the suture which unites the two halves of the hard palate in the midline. Because the condition, though fairly common, has not received much consideration in the medical literature, LANE (*J. Am. Med. Assn.*, 1927, **88**, 1966) briefly reviews its salient features and illustrates it by means of a picture. Clinically, the malformation has but little import, although it has been suspected as being sarcoma, syphilitic periostitis or gumma.

Chronic Tonsillitis. Microscopic Pathology.—After describing the various lesions encountered in the microscopic study of about 2000 pairs of tonsils, giving some new features and emphasizing some old ones, NELSON (*Arch. Otolaryngol.*, 1927, **5**, 249) draws a composite picture of his findings. The first response to tonsillar infection consists of an inflammatory reaction and leukocytic migration into the epithelium and space of the crypts, and of a hyperplasia of the lymphoid follicles. A prolonged encounter between the invading bacteria and the leukocytes destroys the cryptic lining, resulting in the formation of granulation tissue. By proliferation and contraction of these granulations an attempt is made to obliterate the septic area from below outward, but the depth and ramification may pervert this process so that purulent pockets are obstructed or walled off to form abscesses. Fibrosis of the stroma commences to strengthen the barrier but this in time destroys the active elements without extruding the infectious material. As the capsule and the peritonsillar tissues become involve in the chronic inflammatory reaction, fibrosis and thickening occur, and cartilaginous and bony walls of defense may develop. However, these barricading efforts of nature seldom succeed in expelling the invading hosts from the cryptic labyrinth, although complete destruction of the essential tonsillar structure and extensive degenerative changes may be produced. Despite the less complex nature of the adenoidal crypts, their dependent position and tendency to protrude, actual chronic inflammation, as evidenced by ulceration in the crypts and the formation of granulations and purulent exudate, was sometimes encountered in the adenoids as in the tonsil.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Heliotherapy in Chest Diseases.—In cases of postoperative pulmonary abscess and empyema, SINGER (*Arch. Phys. Therapy., X-Ray, Radium*, 1927, **8**, 240) found that after a few applications of the light the pus was diminished in amount, the skin, which was often macerated about the edges of the wound, became dry and clean, the odor became less or disappeared, and, in a general way, the patients felt better, their appetites improved and they gained weight. When the sun is not available the ultraviolet lamp gives good results.

Iodized Oil and Pneumoperitoneum in Gynecology.—STEIN and ARENS (*Radiology*, 1927, **8**, 497) consider iodized oil to be of value in depicting the uterine and tubal lumina. Its chief value lies in locating the site of tubal obstruction. The information it yields concerning uterine pathology is often incomplete because uterine disease alters the contour of the organ more than its lumen. Iodized oil is practically useless in the diagnosis of ovarian disease. Iodized oil and pneumoperitoneum combined yield the maximum information regarding the pelvic organs short of exploration, and are indicated in a carefully selected group of cases.

Metallic Colloids in the Treatment of Cancer.—After trials with colloidal lead by Bell's method, which produced alarming toxic effects in the majority of patients, ULLMANN (*Radiology*, 1927, **8**, 461) on the suggestion of Bischoff, has tried lead orthophosphate. Experiments on rabbits indicated that the orthophosphate had no deleterious effect on the hemoglobin. It was then given to patients suffering from cancer. Toxic effects so far have been negligible. Hemoglobin and blood count were moderately reduced in some cases, but in 1 case cited both were increased. The time has been too short to draw conclusions, but the apparent clinical effect on the tumors—initial pain and swelling followed by reduction in size—seems to be as marked as after the administration of the metallic colloid. SOILAND, COSTOLOW and MELAND (*Radiology*, 1927, **8**, 469) report 12 cases treated with colloidal lead after the method of Blair Bell. Only 2 of these showed any apparent improvement. All the others became progressively worse, and in 2 cases death was undoubtedly hastened. All of the cases were apparently hopeless insofar as any other treatment was concerned. The lead is highly toxic, and even in amounts approximately one-half of those used by Bell, the effects were extremely grave. Discussing the fore-

going papers, Bolliger said that the lead treatment had been used in 12 cases at the Henry Ford Hospital. Among the 12, none died acutely, and none of the deaths was due to lead poisoning. So far there are no cures, but 1 case of rapidly-growing squamous-cell carcinoma seems to be definitely arrested.

Present Status of the Roentgen Ray in the Diagnosis of Pulmonary Tuberculosis.—In a well-written editorial, AMBERSON (*Am. J. Roent. and Rad. Therap.*, 1927, **17**, 557) compares the roentgenologic diagnosis in the past of pulmonary tuberculosis and that of the present. In the ardor of its youth, roentgenology begot some monstrosities. One of these was "peribronchial tuberculosis," an interpretation based on an arborization of the hilum with beading or stippling along the trunks. For a season the propriety of this diagnosis was not questioned. Many of these patients were sent to tuberculosis sanitariums. In 1918, no less than 13 per cent of the patients at Trudeau Sanitarium were classified as "peribronchial tuberculosis," although tubercle bacilli were found in but 1 of the 34 patients. If general symptoms were present they were mild and the anticipated mortality did not materialize. Among the cases traced none died of tuberculosis. On the clinical side there is nothing to speak for the existence of "peribronchial tuberculosis," but much against it. It was probably "peribronchial tuberculosis" which moved Osler to remark in one edition of his textbook: "More than any others, radiographers need the salutary lessons of the dead house to correct their visionary interpretations of shadows, particularly of those radiating from the roots of the lungs." But all this has largely been relegated to the past. The studies of recent years have evoked a working rule that appears sound. This is epitomized in the National Tuberculosis Association's "Diagnostic Standards" as follows: "Definite (roentgenographic) parenchymal changes are seen in nearly all instances of proved pulmonary tuberculosis. Absence of such changes demands other proof of the existence of the disease." It is specified that tuberculous lesions are located usually in the upper half of the chest. If, in the absence of these changes which proclaim themselves in the roentgen film as "mottling," "cirrhose clouding," or gross nodulation in the outer and upper part of the lung field, the roentgenologist refrains from making a diagnosis of clinical pulmonary tuberculosis, he will not often be in error, Other evidence of a clinical sort may be strongly suggestive of tuberculosis, but, unless pulmonary infiltration is demonstrable by Roentgen rays, or other proof is forthcoming, the clinician must look farther afield.

Actinomycosis of the Lungs.—While actinomycosis has its most frequent location about the jaw, TURNER (*Radiology*, 1927, **7**, 39) states that the lungs are third in order of involvement. Because of the fact that the early tissue reaction toward the organism is fibrosis and granulation, the radiologist is likely to discover the first evidence in the primary lung cases. The organism is not found in the sputum until there is breaking down of a granuloma with drainage into a bronchus. From the radiologic point of view, there are two types of actinomycosis of the lungs; in one type the infection involves the hilus and extends along the bronchi, producing peribronchial infiltration with extensive fibrosis;

the other involves the parenchymatous tissue and presents a picture of abscess. A tendency of the disease is to develop new foci separated from each other by normal tissue. Either type results in an abscess which is more rapidly progressive than an abscess resulting from tuberculosis or pneumonia. By examinations at intervals of about two weeks this rapid progress can be noted. Another roentgenologic simulant of actinomycosis is syphilis, but this is likely to produce a fan-shaped shadow radiating from the hilus, the lesion progresses slowly and clinical symptoms are slight, whereas, in actionomycosis the symptoms, including, fever, are marked. Actinomycosis is not distinctive roentgenologically, and the diagnosis can be established only by coöperation of radiologist, clinician and microscopist. The diagnosis is usually completed when the organism is found in the sputum, but it is to be remembered that the ray fungus is frequently present around carious teeth and may thus find its way into the sputum. Turner reports a case of actinomycosis in the right lower lobe near the diaphragm. The abscess appeared first as a moderately dense homogeneous shadow, which later cleared at the center as evacuation took place, the walls remaining evident.

Diabetic Tuberculosis.—In 1923, following observation of several diabetic patients with a florid hilum type of tuberculosis with few or no physical signs, SOSMAN and STERDL (*Am. J. Roent. and Rad. Therap.*, 1927, **17**, 625) began a study of this association. All incoming patients with diabetes were given a routine Roentgen examination of the chest, and during the past three years 182 cases of diabetes have been observed. Pulmonary tuberculosis was revealed in 9 per cent of the cases. In over a 1000 cases of diabetes observed in the same hospital, pulmonary tuberculosis was noted clinically in only 3 per cent, while in a series of 37 necropsy cases it was dicovered in 19 per cent. The discrepancy may be accounted for by the fact that symptoms of tuberculosis are often mild and may be overlooked clinically, or by the fact that tuberculosis is frequently superimposed on diabetes as a terminal infection. The tuberculosis was frequently of the hilum or unsensitized form—46 per cent of the 45 cases—and occurred mostly in patients past forty-five years of age. The prognosis was uniformly poor, even with insulin.

Treatment of Nerve Palsies.—Of the various physicotherapeutic methods employed in the treatment of palsies, ELSOM (*Arch. Phys. Therap., X-ray, Radium*, 1927, **8**, 299) emphasizes the following: Massage, to maintain tone and to increase circulation, but using it for short periods and without violence; heat in its various forms; voluntary corrective exercises, both active and passive; careful use of galvanism and faradism in peripheral nerve palsies, preferably the slow sine wave; proper hygiene, including abundant diet, sleep, fresh air, sunshine or its substitute, the ultraviolet rays, and above all, patience and persistence in the treatment. In Bell's palsy, Elsom advises the application of heat to the affected side. Hot-water bags to the face, especially at night, should be used. The forms of radiant light and heat are very useful, especially the infra-red radiations. In addition, diathermy should be employed followed by mild galvanic stimulation. Treatments

are best given daily or at least three times a week. In the acute stage of anterior poliomyelitis, isolation, rest in bed, sometimes counter-irritation to the spine by means of mustard or high-frequency sparks, diaphoresis by hot packs, and warm baths are indicated. In the chronic stage full diet, massage, active exercise, and perhaps diathermy to the spine are advised. Elsom cautions against violent massage and strenuous exercise, and considers galvanism and faradism to be undesirable in anterior poliomyelitis.

Lymphoblastoma of the Orbit.—Among 500 cases of lymphoblastoma (Hodgkin's disease) at the Massachusetts General Hospital, REEVES (*Am. J. Roent. and Rad. Therap.*, 1927, **17**, 642) found 7 in which the primary or sole focus was in the orbit. All patients except 1 were under forty years of age. The first symptom noted was either a firm freely movable mass in the orbital tissues or exophthalmos. No patients had pain. Four had intrabulbar involvement and the affected eye was enucleated. Several were treated with Roentgen ray or radium, and became practically well; only one developed generalized lymphadenopathy. Radiotherapy had no injurious effect on the lens. The condition should be thought of in all cases of extra- or intrabulbar tumor.

Interpretation of the Pyelogram.—NICHOLS (*Radiology*, 1927, **6**, 469) reviews some of the characteristic lesions of the kidney which may be determined by pyelographic examination. Anomalies must always be considered. In the embryonic pelvis the shadow is like a miniature of that of the normal pelvis. An anomalous pelvis may have multiple calyces, even seven or more, but these have the normal outline. An elongated cephalic calyx is not uncommon. Hydronephrosis in an early stage is to be suspected when the minor calyces are obliterated and the calyces and pelvis are dilated. The degree of hydronephrosis is no criterion of the severity of the obstruction. The pyelogram does not disclose an empyemic kidney. Pyelonephrosis is not evident on the pyelogram unless a perinephritic abscess has formed and has ruptured into the pelvis or ureter. Clubbing of the calyces and moderate dilatation are early evidence of chronic pyelitis; later, contraction may take place, producing a small distorted pelvis. Pyonephrosis is evidenced by a dilated pelvis and calyces, by areas of necrosis shown by abscess cavities, by areas of connective-tissue repair in the kidney, and by enlargement of the kidney. Tuberculosis of the kidney is a pyonephrosis and may show a characteristic irregular pyelographic outline with an ostrich-plume appearance. Phosphatic stones in the kidney pelvis usually assume the shape and size of the pelvis; if they are spherical they may simulate tumor. Adenocarcinoma and hypernephroma usually originate in the pole of the kidney and encroach on the calyces, or they may involve the pelvis and produce long spindle-shaped calyces with clubbed ends. Papilloma deforms the pelvis and may be accompanied by stone or hydronephrosis due to transplants in the ureter. Polycystic kidney is usually not pyelographed, but when this is done, characteristic cystic areas encroaching on the pelvis are seen. A solitary cyst, if large, encroaches on the terminal calyces.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Encephalitis Periaxialis Diffusa—Report of Three Cases with Pathologic Examinations.—STEWART, GREENFIELD and BLANDY (*Brain*, 1927, **50**, 1) present cases of Schilder's form of encephalitis periaxialis diffusa. They show considerable variation between each other and other reported cases, but on the whole the picture is quite definite. The authors call particular attention to the following facts: On the clinical side, that the disease may kill with great rapidity (nine days in one case) and that the first symptom may be deafness of central origin preceding all other symptoms by some months. On the pathologic side, the disease is not necessarily, nor perhaps usually, confined to the centrum ovale, but may affect the other parts of the central nervous system. The diagnosis between this disease and multiple sclerosis is very difficult at times and rests clinically on the progressive and ultimately total blindness and deafness and on its bilateral aspects in Schilder's disease. Pathologically the pictures are very similar and may lead to erroneous histologic diagnosis.

Method for Demonstration of Spirochæta Pallida in Single Microscopic Sections.—DIETERLE (*Arch. Neurol. and Psychiat.*, 1927, 18, 73) states that previous methods of demonstrating Spirochæta pallida have been unsatisfactory. The advances made over the Levaditi method by Manouelian, Noguchi and Jahnel have led to the author's method, which depends on the already recognized principle that impregnation of nerve fibers could be prevented by use or uranium salts. He presents a new modification of the procedure with a detailed description of technique and believes this method more reliable and simpler than former methods. Place fixed and cut preparations in 1 per cent solution of uranium nitrate in 70 per cent alcohol for a half hour. Wash in distilled water and pass through 96 per cent alcohol and then transfer individually to 10 per cent gum mastic in absolute alcohol for about thirty seconds and pass through 96 per cent alcohol again. Transfer to distilled water. Silver, one to six hours, in 1 per cent aqueous silver nitrate in the dark. Wash in water. Develop in a special reducing solution. Wash in distilled water. Transfer to 96 per cent alcohol and then to acetone to dissolve out the mastic and dehydrate. Clear the xylene and mount in Canada balsam.

Acute (Epidemic?) Encephalitis—Report of a Case in a Newborn Twin with Histologic Observations.—HASSIN (*Arch. Neurol. and Psych.*,

1927, **18**, 44) reports a case of acute encephalitis in a child dying at the age of fifteen days. The diagnosis is not beyond question, but seems most probable. The pathologic picture was similar to that seen in experimental encephalitis in animals and not the typical picture seen in man. However, it resembled quite closely DaFano's case. The author concludes: "Had the child recovered with the disease unrecognized or not even suspected, some sequelæ, such as epilepsy, mental deficiency, idiocy or behavior disorder, would be expected. In other words, any of these or similar disorders observed in grown children may be caused by inflammatory brain lesions occurring in early infancy." (One would expect, rather, in this case the usual sequelæ of encephalitis. While there is no proof that epilepsy would not result from such a lesion, it would be rather surprising to find it.)

Manganese Toxemia: With Special Reference to the Effects of Liver Feeding.—CHARLES (*Brain.*, 1927, **50**, 30) reports that the diagnosis of manganese toxemia is not difficult as the picture is strikingly characteristic. Experimentally it was found by G. Marshall Findlay that manganous chloride produced cirrhosis of the liver in rabbits, rats and guinea-pigs. The clinical manifestations of manganese toxemia are similar in many respects to those of progressive lenticular degeneration, which disease is associated with cirrhosis of the liver. Barnes and Hurst have described 4 cases of hepatolenticular degeneration which seem to prove that the nervous symptoms do not occur until the liver has become grossly diseased. Various explanations have been offered, assuming that the neurologic lesion is due in some way to the cirrhosis. The author assumes that it might be due to the absence of a hormone. Seven cases of manganese poisoning are presented which were treated with feedings of raw liver with some benefit in a few cases. Case II is very suggestive of a connection between the treatment and the improvement shown in that during a lapse of five years without treatment he had not improved, whereas during treatment he showed considerable improvement. Several of the cases showed hepatic deficiency by the levulose test.

Intradural Spinal Lipoma.—STOOKEY (*Arch. Neurol. and Psychiat.*, 1927, **18**, 16) reviews the literature on reported cases. Up to 1926, 9 cases of uncomplicated extradural and 9 of intradural spinal lipoma had been reported. In the cerebral meninges the tumors are much more common. Two theories of origin have been advanced: (1) Occasional fat cells in the pia give rise to the tumor; (2) the tumor arises from inclusions of embryologic rests within the meninges at the time the neural tube is formed. The tumors are commonly associated with congenital abnormalities. All but one of the intradural spinal lipomas have been pure lipomas, the only mixed one being a myolipoma. That intradural lipomas may be congenital speaks somewhat for the theory of embryologic rest inclusions. Mesodermal inclusions are difficult to understand, but may be possible. Another source might be mesenchyme carried into the neural wall to form the foundation of the blood supply. It is possible that these tumors are primarily intramedullary and only become secondarily extramedullary. Another viewpoint might be that the primitive tendency of the spongioblast and ependymal

cells to accumulate fat and form myelin may be continued abnormally. As to operability, the removal of these tumors has not been possible. The better procedure would seem to split the capsule and perform a decompressive laminectomy. The author further discusses the diagnosis and presents a case of intramedullary lipoma of the cervical cord extending from the second cervical to the fourth thoracic vertebra. When operated on removal was found impossible and a decompression was performed resulting in almost complete recovery.

Fungal Pruritus Vulvæ.—One of the most distressing though not serious conditions from which the female may suffer is the intolerable itching of the genitalia which is termed pruritus of the vulva and anus. In teaching our students to treat this condition, we tell them to find the cause and eliminate it. There are so many possible causes of this condition that each case must be carefully studied for its particular etiologic factor. In describing a type of fungal origin, CASTELLANI (*New Orleans Med. and Surg. J.*, 1927, **79**, 625) states that it is little known although in his experience of fairly common occurrence. The usual cause is a fungus of the genus Epidermophyton, the same type which causes tinea cruris and toe phytosis. A definite diagnosis cannot be made without finding the fungus microscopically but a probable diagnosis can often be made clinically, since the minute, red, infiltrated patches in the affected area are very suggestive especially if the patient is suffering from mycotic dermatitis of the toes or gives a history of having suffered from dhobie itch or tinea cruris in the past. The course of the condition is chronic, but periods of great improvement and apparent cure may alternate with periods of severe recrudescence. In the treatment of this condition, he has had very good results by using an ointment containing 30 gr. of precipitated sulphur and 30 gr. of salicylic acid to the ounce of vaseline. Other useful preparations are Deek's ointment consisting of salicylic acid, 4 parts; bismuth subnitrate, 10 parts; mercury salicylate, 4 parts; oil of eucalyptus, 4 parts; vaseline and lanolin, sufficient to make up 100 parts; also a slightly modified Whitfield's ointment consisting of carbolic acid, 5 gr.; salicylic acid, 15 to 30 gr.; benzoic acid, 15 to 30 gr.; vaseline, 1 ounce. When the pruritus is unbearable, painting the parts with a lotion consisting of 15 gr. of silver nitrate to the ounce of spirits of nitrous ether, at times stops the itching, either immediately or after a short period of time during which the pruritus may become intensified. In very chronic cases Roentgen ray treatment is to be recommended although it is not always successful.

Decerebrate Rigidity Following Encephalitis: Report of a Case with Necropsy.—WEISENBERG and ALPERS (*Arch. Neurol. and Psychiat.*, 1927, **18**, 1) reports a case of decerebrate rigidity in man following encephalitis. Pathologically, inflammatory and degenerative changes were found in the nucleus ruber. The authors review the cases of decerebrate rigidity already reported with a critical discussion. They then proceed to a discussion of the theoretical interpretation of decrebrate rigidity in man. They agree with Weed, Brown and Wilson, in attributing to destructive lesions in the nucleus ruber an important role in the production of decerebrate rigidity."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Questions and Answers on Smallpox and Vaccination.—LEAKE'S (*Pub. Health Rep.*, 1927, **42**, 221) paper was prepared in response to requests for data on variola and vaccination; the more important points are quoted as follows:

"*What is the Best Method of Vaccination?* Probably the 'multiple pressure or prick' method. This consists of a shallow, tangential pricking of the cleansed, but not irritated, skin with a needle, through a drop of smallpox vaccine, covering an area not greater than $\frac{1}{8}$ of an inch (3 mm.) in diameter. This gives little chance of accidental infection and the eruption is typical. Acetone has been found satisfactory for cleansing the skin. It is somewhat more efficacious and rapidly drying than alcohol. The needle, which should be new, sharp, and sterile, is not thrust into the skin, but is held quite parallel or tangential to it, with the forefinger and middle finger of the right hand above the needle and the thumb below, the needle pointing to the operator's left. The needle should be crosswise of the arm so that the thumb of the operator is not impeded by hitting the skin. The side of the needle point is then pressed firmly and rapidly into the drop about 30 times within five seconds, the needle being lifted clear of the skin each time. This rapid to-and-fro motion of lifting the needle and pressing it against the skin should be quite perpendicular to the skin and needle, and not in the direction of the needle. In this way the elasticity of the skin will pull a fraction of an inch of the epidermis over the point of the needle at each pressure so that the vaccine is carried into the deeper epithelium (cuboidal prickle-cell layer), where multiplication takes place most easily. If the skin has not been unduly rubbed in cleansing, and if the motion is entirely perpendicular to the needle, no signs of bleeding will occur and all evidence of the punctures will fade out in less than six hours. Immediately after the punctures have been made the remaining vaccine is wiped off the skin with sterile gauze and the sleeve pulled down, the whole operation of puncturing and wiping taking less than ten seconds. With strong vaccine a single pressure not infrequently gives a 'take.' Only 6 pricks or punctures were formerly advocated; comparative tests showed this to be inferior to the scratch method in percentage of 'takes.' By the use of 30 pricks this difficulty has been overcome, and the percentage of 'takes' is as high as with any other safe method."

"*What is the Best Vaccination Dressing?* None at all. The ideal to be sought is to keep the site cool and dry, so as to promote rapid formation of a firm crust and to avoid maceration and rupture of the vesicle. Heavy or tight clothing, perspiration, and even repeated washing with alcohol interfere with rapid desiccation. If necessary to prevent soiling of the clothing, a fold of sterile gauze may be attached to the garment, not to the skin. Occasionally a severe take may require a few days of antiseptic dressings; primary vaccinations should be inspected about the fourteenth day to insure that desiccation is proceeding properly. There is no objection to a light sterile dressing for the first few days after vaccination, provided the arm is under constant competent surgical attention and maceration is prevented, but such provision is seldom assured."

"*Are There Any Objections to Vaccination on the Leg?* Yes. Leg vaccinations are exposed to more moisture, and to more contamination from street dust, than vaccinations at the region of the deltoid insertion."

"*Is Early Surgical Treatment of the Vaccination Vesicle Satisfactory, Such as Opening and Applying Antiseptics?* Yes; provided constant, competent care is exercised thereafter until healing is complete. However, the maximum immunity is not obtained until the red areola has reached its greatest diameter and begun to fade."

"*Are Any Other Methods of Vaccination and Treatment Satisfactory?* Any method is satisfactory which insures that the vaccine is deposited in the deeper layers of the epidermis with no more injury and over no greater an area than by the pressure method (not longer than $\frac{1}{8}$ inch or 3 mm. in any direction), and which avoids poulticing the developing vaccination. With any scarification method, to secure the maximum number of 'takes' possible with the virus used, the vaccine should be rubbed in with the side of the scarifier or with a sterile toothpick for at least fifteen seconds."

"*Are There Any Objections to the Intracutaneous Injection of Diluted Vaccine Virus?* Yes. It is likely to be more painful than the method described above, and in many instances, even in good hands, the injection will be subcutaneous rather than intracutaneous; subcutaneous applications of smallpox vaccine give reactions which are different from ordinary vaccinia and are not to be differential from reactions following other injections, so that one is never sure of the potency of the vaccine being used."

"*How May the Various Reactions following Smallpox Vaccination be Differentiated?* By observation two days after vaccination and twice later, about four and eight days after vaccination, and by the coöperation of the person vaccinated to observe when the maximum reaction is reached. With a reaction of immunity, which indicates full protection against smallpox, the broadest redness is reached and passed in eight to seventy-two hours after vaccination. This redness is accompanied by a slight elevation of the skin, which can be felt by passing the finger lightly over the vaccinated area. With the accelerated or modified vaccination or vaccinoid, which indicates partial immunity, the broadest redness is reached and passed in three to seven days after vaccination. With a typical primary vaccination, indicating absence of immunity to smallpox prior to this vaccination, the zone of redness, rather narrow from the third to the seventh day, begins a sudden spread about seven

days after vaccination and reaches its broadest diameter in eight to fourteen days after vaccination, rapidly disintegrating and disappearing thereafter. These three types merge into each other, all gradations being found in practice; differentiation into the three types is based on the time of broadest redness. The prompter the maximum the higher is the immunity. Vesicles are formed in vaccinoid and typical vaccinia reactions, but not with the reaction of immunity."

"*What Untoward Results from Vaccination are to be Looked For?* With aseptic technique and a small insertion site which is kept dry and cool, the great majority of vaccinations go through their typical course and heal promptly if the crust is left undisturbed. Rarely, due possibly to skin bacteria which cannot be removed by the preliminary cleansing, the vesicle will become purulent and extend beyond its normal diameter, which is not over $\frac{3}{8}$ of an inch (10 mm.) greater than that of the insertion site, the drying up of the vesicle and the fading of the areola being thereby delayed. Opening of the pustule and the temporary application of some strong antiseptic, such as mercury bichlorid solution, should be practiced if this takes place. Accessory vesicles around the vaccination site may in some cases be caused by too vigorous cleansing of the skin prior to vaccination. The virus may also be transferred to scratches or other skin lesions, giving rise to distant vesicles."

"*How Can One Tell Whether the Vaccine Used is of Full Potency?* A fair test that the vaccine is of full potency is that when properly applied it gives 100 per cent of vaccinias (typical 'takes') in every application on at least 100 previously unvaccinated individuals. A more practical test is that it should give more than 50 per cent of vaccinoid reactions in persons who have been vaccinated or have had smallpox over ten years previously, and immunity reactions or typical vaccinias in the remainder; a much smaller number of individual vaccinations will give a good idea of the potency of a batch of vaccine by this test."

(*To be continued in December issue*)

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